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PREVENTIVE MEDICINE IN BRITAIN

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PREVENTIVE medicine in Britain was first concerned chiefly with environmental hygiene. The years 1875 to 1900 covered a long series of progressive reforms under the direction of the Local Government Board, which supervised such local government as related to public health and relief of the poor.

These reforms comprised general sanitary improvements, pure water supplies, pure food supply, provision of isolation hospitals for infectious diseases, public vaccination, the supervision of slaughter-houses and common lodging-houses, and others. Local authorities obtained control over housing, powers to condemn slums, and to provide new housing accommodation. Infectious diseases were made notifiable, while port sanitation prevented the admission of fresh disease and plague and pestilence into Britain.

These measures were followed by a great improvement in Britain's national health. The water-borne diseases have become almost negligible. Cholera has been abolished and typhoid is now a rarity, though watch is still kept for epidemics caused by "carriers." Personal cleanliness and lessened overcrowding have stamped out typhus, the deadly "jail fever," which spread from the prisoner in the dock to the judge on the bench. Every second person is no longer scarred with smallpox.

The great advances made in medical and natural science contributed largely to administrative progress. For this was the age of Darwin, Huxley and Lister, of Pasteur, Simpson and Koch, of Stephenson and Watt, the first who ever burst into those silent seas of knowledge and revealed new learning in biology, antiseptic surgery, bacteriology, anesthetics and engineering science. The skill and experience of many have all been assembled to constitute the science of public health.

The succeeding trend of preventive medicine from the reign of King Edward VII onwards has been in the direction of preventing the contraction and transmission of disease in human beings. Progress in environmental hygiene has not stood still. There have been a number of Housing and Town Planning Acts and factory legislation.

From 1919 to 1938 the number of new State-aided dwelling houses was about $1\frac{1}{2}$ million, and private enterprise, without subsidy, produced nearly $2\frac{1}{2}$ million houses, so that 4 million new houses have rehoused about one-third of Britain's whole population. The housing policy of the State has a three-fold objective: (1) the eradication of the slums; (2) the abatement of overcrowding; and, (3) the provision of new houses at as low a rent as possible.

Workers in mines and factories now pursue their avocations in a healthier atmosphere; there is less risk of disease, crippling and death; and lead and other forms of poisoning in industrial processes, as well as silicosis, have been greatly diminished.

Preventive medicine in Britain enlarged its activities some 30 years ago by taking the individual in hand, by promoting facilities and education for keeping him healthy, and by treating his disease in order to safeguard the community.

The State made an important contribution to this wider interpretation of public health by introducing school medical inspection in 1907. Medical inspection of school children has separated the impaired and defective child from the normal and healthy. Arrangements have been made for attending to the health of both sick and healthy children. Many morbid conditions have been reduced, the general physique of school children has improved, and in addition to direct medical results, the teaching of hygiene and cleanliness, the physical training and the provision of milk and school meals have reformed the physical condition of the children of Britain beyond all comparison with the past. A health conscience is developing both in the children and their parents.

During the past 30 years the larger authorities—the counties and county boroughs—have been given much greater powers as guardians of the public health. They were made responsible for the individual health services, the maternity and child welfare services (for the most part), the public assistance medical service for necessitous persons, the tuberculosis and venereal diseases services, the cancer service, the orthopedic service, the hospital services (including, to some extent, pathologic services), and the mental hospitals service.

Britain's Ministry of Health initiated these services by promoting legislation which made them a duty of the county councils and county borough councils, and by administering Government Grants to aid them. The cost of the services is thus defrayed partly by the State and partly by local rates. The Ministry lays down the lines on which these services are administered by the local authorities, approves the scheme of work, inspects the services through its medical officers, and by health surveys sees that a proper standard of efficiency is maintained, having regard to the individual authority's resources and needs. But the actual work is done by the county council and the county borough council with the advice of their medical officers of health.

Britain's National Health Insurance Medical Service, set up in 1911, is of primary importance in confirming the rôle of the medical practitioner as the first line of defense in combating disease. Normally, some 17,000 medical practitioners in England and Wales are engaged

in this health service. It provides a means whereby the industrial workers of the country can have ready access to medical advice, not only for actual ill health, but for those who need guidance to keep their health. The Service is administered centrally by the Ministry of Health and locally by Insurance Committees.

In Wales the Welsh Board of Health is part of the Ministry of Health, while the Department of Health for Scotland exercises similar functions to those of the Ministry.

Two world wars seemed likely to set back the hands of the clock of social progress in Britain. But let us look at some comparative vital statistics. The death-rate for England and Wales about the year 1900 was 18 per 1000, whereas since 1918 it has been in the neighborhood of 12 per 1000. In 1938, the last unbroken year of peace, it was 11.6 per 1000 persons.

Tuberculosis is a disease whose ravages are prone to affect the youthful and adolescent as well as the adult members of the population. The death-rate from tuberculosis serves as a convenient index of the success of public health measures. At one time tuberculosis occupied first place among the principal epidemic or general diseases as a cause of mortality. It has fallen from that disgraceful pride of place. During the 25 years before 1936 the standardized death-rate from pulmonary tuberculosis declined by 49%, and for non-pulmonary tuberculosis by as much as 69%.

The crude death-rate from all forms of the disease was 635 per million, the lowest figure yet recorded. In the decade 1911 to 1920 the number of deaths each year from tuberculosis (all forms) was about 52,000, "a thousand funerals a week." In 1938 this figure was only 26,176, or nearly half the average figure in 1911 to 1920.

In the period 1896 to 1900 the infant mortality-rate (that is the death-rate of infants under 1 year of age per 1000 born) was 156. In 1938 it dropped to the then record figure of 53.

The maternal mortality-rate, which for many years had averaged over 4 per 1000 live births, began to decline in 1936 and by 1938 had reached the then record figure of 2.97. This fall coincided with special measures undertaken for the care of women in childbirth and with special chemotherapy for puerperal sepsis.

These are salient examples of the improvement in national health brought about by preventive medicine. In 1939, when Britain was forced into totalitarian war, the people marched into battle fortified by better physique and better health, the gifts of medical and public health progress.

War favors disease, and the task before the State and health authorities both before and in the early years of the war was a stupendous one. Important and extensive as public health responsibilities were during the last war, they are vastly increased in the warfare of today. The discoveries of science have placed more powerful weapons of destruction in the hands of man. The aeroplane flies bearing death between its wings. The cities of Britain are no longer cities of refuge for invalids, women and children, but may become the most vulnerable centers of attack.

War also exposes populations to the risks of famine and malnutrition, to liability to the contraction of infectious diseases and epidemics through overcrowding, movements of population, increased fatigue and lowering of bodily resistance, and grave apprehensions were expressed that the national health would seriously deteriorate.

With those fateful considerations in mind, the British Government had to take important measures of protection, as well as maintaining the public health services and adapting them to war conditions. Two important measures were the organization of an emergency medical service for the treatment of air-raid casualties and of the wounded, in itself a stupendous task, and the evacuation scheme which included the transfer of school children, expectant mothers, young children, cripples, and blind persons from urban centers to other areas less exposed to German air-raids.

These war schemes at first were far from perfect. In the light of after-events it can be seen that many mistakes were made, many unnecessary plans were devised and there was much waste of effort in preparing for eventualities which never arose. These defects were practically inevitable in a new organization and certainly inevitable in a war which has taken a course very different from the campaigns of the past.

On the whole, however, they met with great success. This was due to careful central planning, to continual overhauling of the machine, and above all to the loyal coöperation of doctors, students, nurses and hospital and social workers of every kind. Britain's Medical Research Council in conjunction with the Ministry of Health set up a comprehensive laboratory service throughout the country. They are also making investigations into war problems of disease such as burns, gas gangrene, blast injuries and others.

Under the capable shield of the allied navies the food supplies of the country are being maintained and the present scale of rationing is equitably administered by the Ministry of Food and is fully adequate for good nutrition.

The prevention of scurvy, scurvy rickets, rickets and other deficiency diseases is included in the economic defense of Britain. Due provision is being made for milk for children and expectant mothers, school meals for children and communal feeding centers. Under the Ministry of Labour and National Service, industrial health is being maintained in factories and workshops with advances in medical and welfare services.

The vital statistics of Britain on the whole continue to be satisfactory. The decline in infant and maternal mortality has been maintained. Two evils, tuberculosis and venereal diseases, both "camp-followers of war," have given some cause for anxiety, but further special measures have been organized to combat them. There have been no large epidemics and any outbreaks that arise are promptly tackled by the health authorities. Diphtheria is still too prevalent, the campaign for immunization against that disease is being urgently pressed and with success.

The sulphonamide preparations are in general use and have reduced the mortality from pneumonia, cerebrospinal fever, puerperal fever

and other diseases to a remarkable degree. Encouraging researches are proceeding on the application of *Penicillin* to war wounds and disease. In brief, British preventive medicine is not only achieving a remarkable and unprecedented success in the present war, but its scope and range are being extended.

It is an encouraging sign of confidence in victory that while Britain is engaged in a life or death struggle for freedom, she can still find time for future planning in public health.

The defects and limitations of the present system are realized, however, and numerous schemes and plans are being ventilated both officially and unofficially. It is the Government's declared intention to fulfill the intentions of Assumption B of the Beveridge Report by establishing a comprehensive medical service. It seems an inevitable condition of such a service that it should be closely associated with the public health services of Britain's local authorities.

For health is more than a question between doctor and patient, valuable as is this relationship. The environment and social conditions of the patient need full attention and preventive medicine must employ a social armamentarium as well as a medical one in order to maintain and improve the public health.

This means a marshaling of all forces—medical, environmental, social and individual to prevent and to combat disease. A notable means to this end is the recent establishment of Chairs of Social Medicine at the Universities of Oxford and Birmingham. Another is the work of the Central Council for Health Education in educating the community in hygiene and the avoidance of disease.

A comprehensive medical service is to be established and a White Paper on the subject just has been issued by Britain's Minister of Health. It may be observed here that the nuclei of such a service are already present in the Insurance Medical Service, the Public Assistance Medical Service, the health services and hospitals of the local authorities, the voluntary hospitals, the specialist provision made by municipal and voluntary agencies and the planning of the Emergency Medical Service. The task is to combine this scattered provision into one harmonious whole. In all these schemes of reform many complicated problems are presented which time, patience and experiment will solve.

CAPILLARY PERMEABILITY IN MYXEDEMA*

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THE presence of edema in the skin of patients suffering from myxedema and the tendency to generalized serous effusions are so far physiologically unexplained. The fact of their presence has been stressed by many observers. The tendency to serous effusions, espe-

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cially in the pericardial cavity, has even impressed many observers so much as to cause them to deny any genuine enlargement of the heart itself, attributing all roentgen evidence of enlargement to pericardial effusions. Feasby² describes a case in which he was able to measure the intrapericardial pressure and to withdraw repeatedly large amounts of fluid from the pericardium. Marzullo and Saverio¹³ describe a case with multiple serous effusions and cardiac involvement which returned to normal after treatment with thyroid. The heart also became considerably smaller after treatment. Lehrman, Clark and Means¹¹ report 5 myxedema autopsies, 4 of which showed *interstitial* edema of the heart muscle and only 2 increased fluid in the pericardial sac. They summarize their findings of the typical pathology as found in myxedema as follows: (1) interstitial edema; (2) fibrosis; (3) pericardial effusion. Hurxthal⁶ also reports cases of myxedema heart with congestive heart failure and polyserous effusions. He states definitely that he attributes the edema to the basic myxedema and not to the subsequent heart failure. Similar findings are reported by Hanssen.⁵ On the other hand, it can be considered well established that the blood flow in the periphery of myxedema cases is considerably diminished. In their extensive studies, Stewart, Deitrick and Crane,¹⁷ Zondek,²⁰ Stewart and Evans,¹⁸ and Macy and co-workers,¹² state that the circulation time in all cases of myxedema is prolonged and that the flow of blood through an extremity is markedly decreased. All these changes return to normal after proper treatment has been instituted. No unanimity can be found in the literature concerning the meaning of the changes in the electrocardiogram. All authors state that there are marked changes in the T waves and occasionally of the P-Q interval in connection with the more or less pronounced general lowering of the voltage. Most of the authors are inclined to attribute the T wave changes to arteriosclerosis, as can be expected with the high cholesterol in the blood; and the changes in voltage to the formation of small or large effusions in the pericardium. Only Lehrman¹¹ and his co-workers state that in all probability the interstitial edema is the main cause for the electrographic changes. Recently, Zondek, Michael and Kaathz²⁰ very clearly stressed the point that the interstitial edema of the heart muscle is, in the majority of cases, the cause for the anginal syndrome. They explain it by the statement that the edema is pressing on the blood-vessels, a contention which one can hardly follow; for the tissue pressure can physiologically never be higher than the pressure in the vessel leading to the area.

A very remarkable finding is published in the literature. Thompson, Thompson, Silveus and Dailey^{18a} found that in myxedema the protein content of the spinal fluid was nearly always markedly increased (up to 242 mg.) and that the globulin test was always positive. The pressure was very often markedly increased. All these findings return promptly to normal on thyroid therapy. They were at a loss to explain these results.

Observers of the capillary microscopic picture in this disease agree that the number of visible capillaries is low.^{14,20}

Starling,¹⁶ in his monograph, "The Fluids of the Body," summarizes the factors causing increased transudation:

A. Increased intracapillary pressure: (a) venous obstruction; (b) vasodilation; (c) plethora.

B. Increased permeability of the vessel wall: (a) local injury by mechanical irritants; (b) local injury by thermal irritants; (c) local injury by chemical irritants.

C. Watery condition of blood (hydremia).

D. Increased molecular concentration of the tissues.

Considering the factor of increased capillary pressure, there is no reason to assume that it is present in myxedema, especially not to an extent as to explain the findings described below. Venous pressure measurements as carried out by Golden and Brauns⁴ have not shown any increase in venous pressure, a finding which is in accord with our own observations. Neither vasodilatation nor plethora is present in myxedema, nor is there any reason to assume a marked hydremia in this disease.

In doing circulation time determinations in patients with myxedema (by means of the fluorescein method reported elsewhere),⁸ it became apparent that these patients had an especially rapid and intense staining of the tissue cells by the dye. Since these patients had a prolonged circulation time and, since we were able to show that in the presence of a normal capillary permeability, slow circulation times were identical with *slow* staining of the tissue cells due to the diminished amount of dye brought to an area, this rapid and intense staining in myxedema patients seemed so remarkable that it stimulated us to the study herein described.

Three attempts have been made so far to attribute the scrous effusions in myxedema to changes in capillary permeability. Neither Gänzlén³ and Peterson¹⁵ with the blister method, nor White and Jones¹⁹ with the pressure plethysmograph have succeeded, however, in proving this assumption. It is probable that in these studies the methods used were not adequate for this purpose and the range of the normal was so wide that no positive results could be expected.

In order to make our observation objective and to be able to estimate its magnitude, recourse was taken to the following method.

Method. The Dermofluorometer,* which is described in detail elsewhere,¹⁰ was used for these observations (Figs. 1 and 2). This device consists of a small but intense light source which, by means of proper filtering radiates a blue light of a short wave length (around 4000 Angstrom units). This light source is rigidly aligned at an angle of 90 degrees to the opening of a sensitive phototube which, in turn, by means of proper filtering, picks up only light waves in the region of green, that means in the region of the fluorescence of fluorescein. The light source as well as the phototube are at a constant distance from an opening in a bakelite plate through which the light shines on the skin of the patient and from which the reflection is picked up by the phototube. The changes in the current output of the phototube, which are dependent upon the fluorescent radiation, are amplified and registered on a measuring instrument. This instrument is calibrated in such a way that an alkaline

* Manufactured for us according to our specifications by the Photovolt Corp., New York City.

fluorescein solution of a concentration of 1 to 30,000,000 in a cuvette of glass permeable to ultraviolet and of 5 mm. depth gives a deflection of one division. This deflection is called *one fluorescein skin unit*.

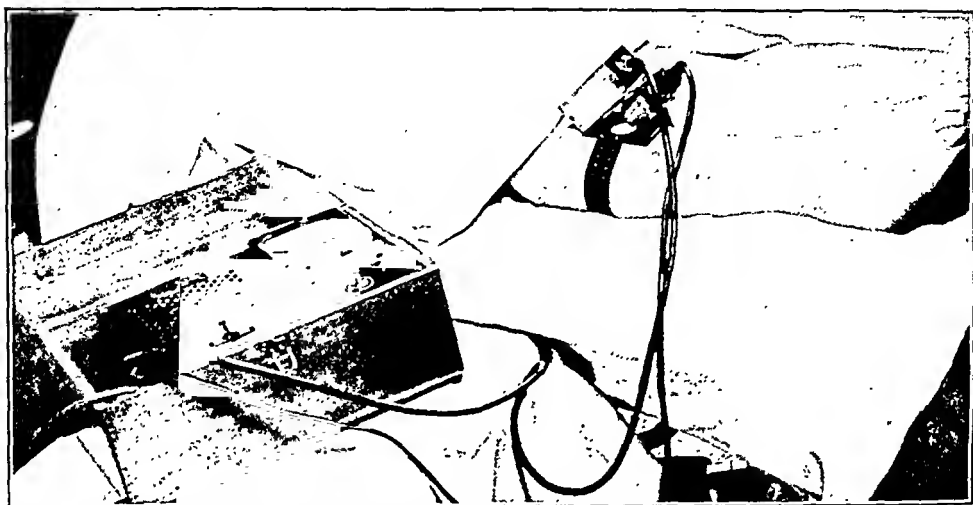


FIG. 1.—The Dermofluorometer attached to the leg of a patient. The search unit is on the skin, the registering instrument on the table.

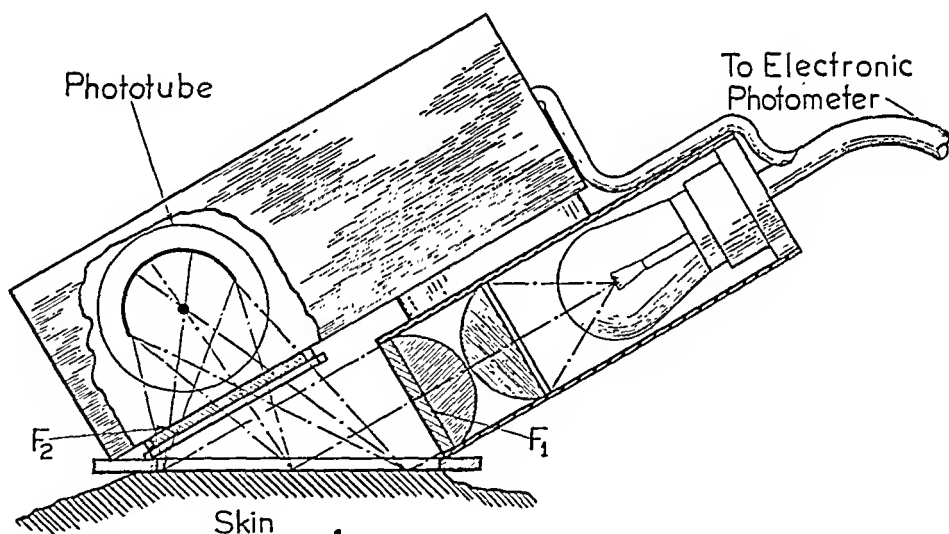


FIG. 2.—The principle of the Dermofluorometer. The light source radiates through the blue filter, F_1 , on the skin. The fluorescence of the skin produced by the intravenous injection of fluorescein is registered by the phototube. Filter F_2 prevents all light except green-yellow from reaching the phototube.

The patient rests for at least 15 minutes before examination in a room with a temperature between 75° and 80° F. Before the examination is carried out, several test spots on the body of the patient are tested with this instrument in a dark room for their illumination. Since the skin in some individuals has a somewhat greenish color, before the injection of any dye these so-called background readings are necessary to eliminate errors. The very low values are noted and later deducted from the values found after the injection of the

fluorescein. One and three-tenths cc. per 10 kg. of body weight of a 5% fluorescein solution to which 5% of sodium bicarbonate has been added are then injected intravenously. The first 4 cc. are given very rapidly while the rest is given within 90 seconds. It may be stressed here that this fluorescein solution is optically 22% more active than a solution of *sodium* fluorescein. The dermofluorometer is attached to the leg of the patient by a rubber strap, while a long wave ultraviolet reflector, such as used for the determination of the circulation time,^{7,9} is beamed on the lips of the patient. Thus the circulation time to the lips and to the leg is being determined objectively.

The degree of deflection registered by the dermofluorometer at the different test spots is read in the beginning every 2 minutes and later every 5 minutes.

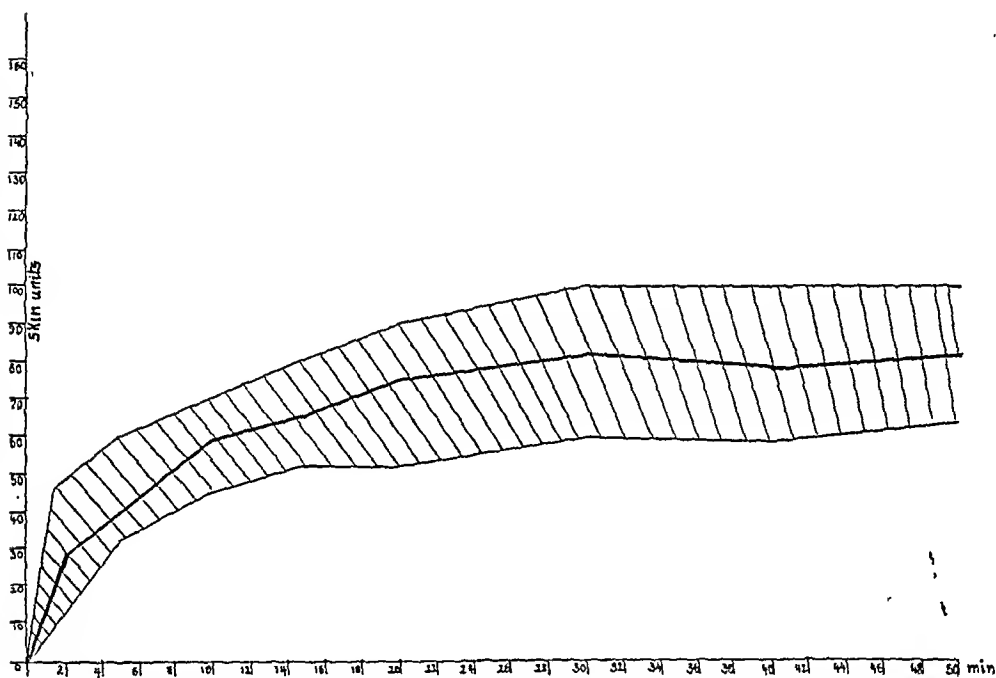


FIG. 3.—The fluorescence values obtained from the legs of 20 normal individuals after the injection of fluorescein. The heavy line in the middle represents the average, the upper and lower border lines, the possible variations in normals.

A curve is thus obtained which is mainly dependent upon 4 factors: (1) the number of capillaries per square inch; (2) the amount of blood streaming through them per time unit; (3) the capillary permeability; (4) intracapillary pressure.

Fluorescein is a very small molecular dye (mol. weight 332). It penetrates practically immediately from the capillaries into the tissue, as can be easily observed under the capillary microscope. It diffuses over the entire length of the capillary loop. In ultrafiltration experiments which represent the experimental counterpart to capillary filtration, it can be shown that three factors influence the amount of fluorescein obtained in the filtrate (tissue fluid): (1) the pore size of the filter (capillary permeability); (2) filtration pressure (capillary pressure); and (3) concentration (blood concentration).

The curves of normals obtained with this method are in a very close range. It was astonishing to see how rigidly the body adheres to its

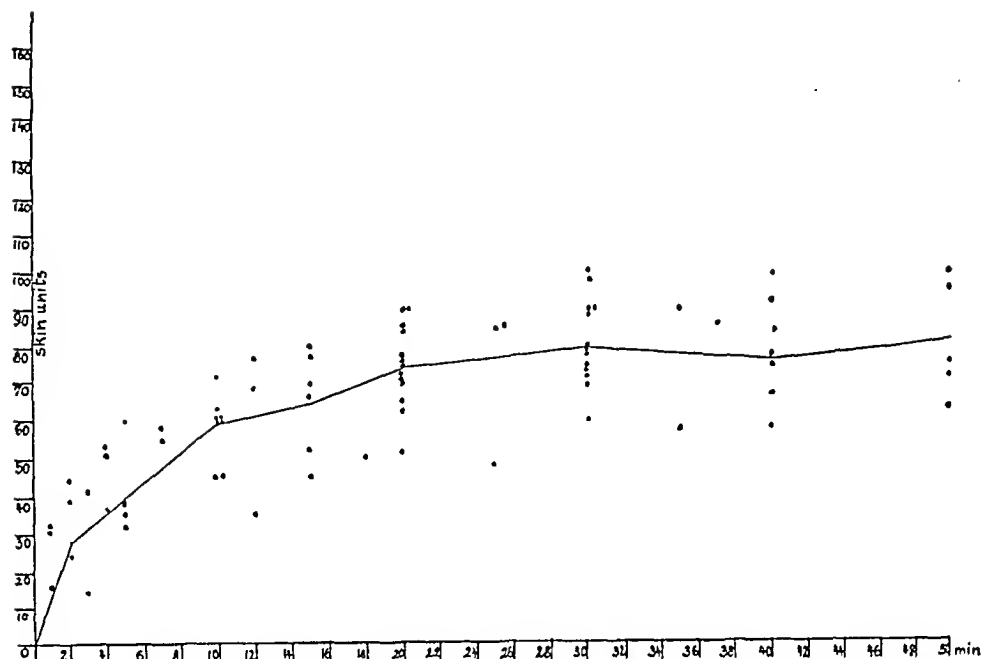


FIG. 4.—The scattering of the values in the permeability curve of 20 normal individuals.

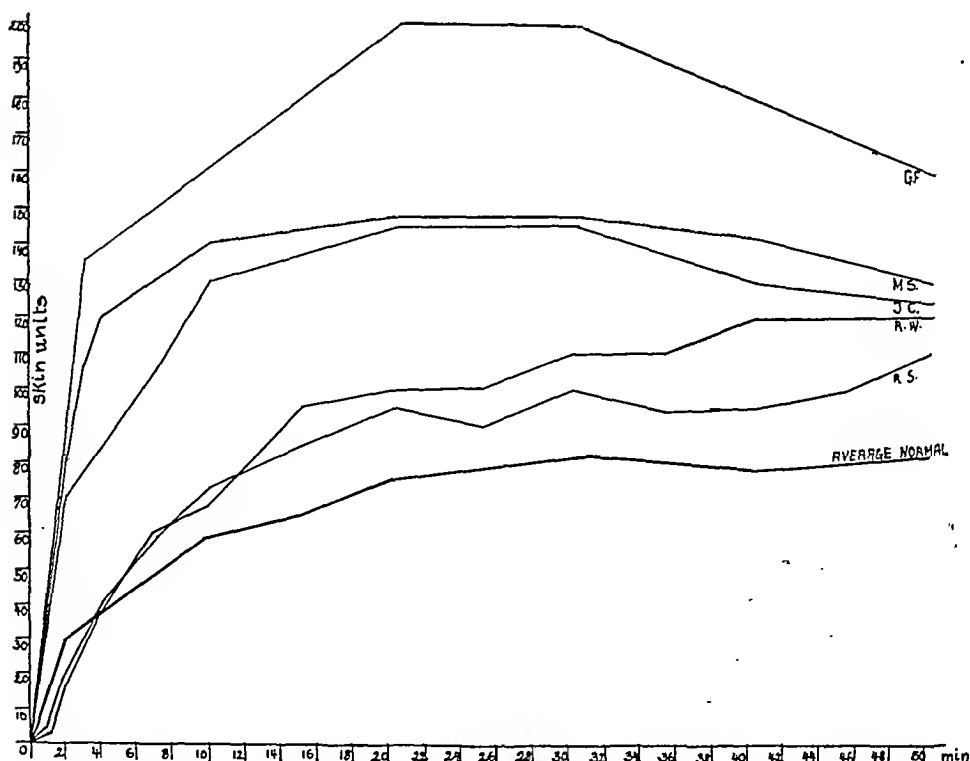


FIG. 5.—The permeability curve as obtained in 5 cases of myxedema after fluorescein injection. The heavy line represents the average normal curve.

permeability curve. We have repeated curves as often as 4 times in the same person at short and long intervals and always observed values within range of $\pm 5\%$. Figure 3 shows the average curve for the normal persons (20 persons). The upper and lower border curves represent the borders of the normal. Figure 4 gives the scattering of the values obtained in these 20 normal persons.

Nine cases of patients in cardiac failure with severe edema showed all curves within normal limits.

Three cases of severe edema in the lower part of the body due to cirrhosis of the liver showed normal curves in all regions.

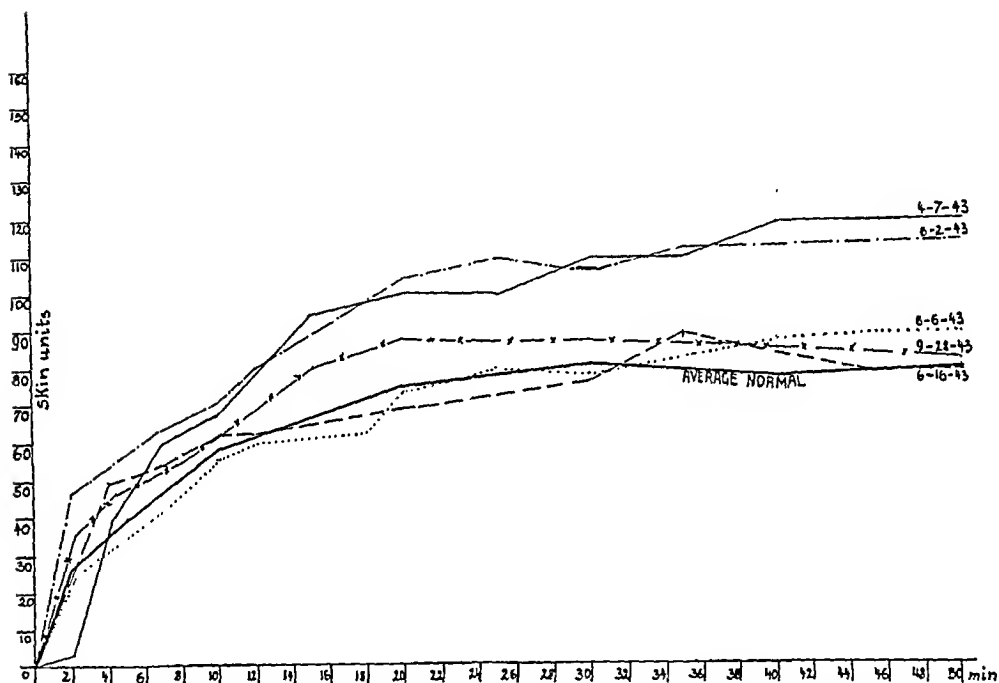


FIG. 6.—The permeability curves of Case R. W. before and after treatment with thyroid. The heavy line represents the average normal curve.

Two cases of severe undernutrition with vitamin deficiencies and generalized edema showed very high fluorescein permeability curves. The most obvious increase in capillary permeability can be noticed in inflammatory reactions. At the side of such a lesion the dye seems to pour out of the capillaries and the area is markedly increased in its fluorescence as compared to the surrounding tissue.

Five cases of myxedema, all in women, were observed. All these cases had a markedly increased fluorescein permeability curve before treatment was instituted. Figure 5 shows the curves obtained from tests on the legs of these patients when they were first examined. It may be stressed here that the curves of all other test spots of these patients were also far above the normal for the regions concerned, and that the leg curves are only chosen as an example since our experience for this test spot is the widest. In 4 cases the circulation time was

more or less prolonged. Table 1 shows all the essential data for these patients at their entrance into the hospital. In all cases the electrocardiogram showed very low T waves in all leads; in 3 of the cases low voltage was present. The heart was markedly enlarged in 3 cases and moderately enlarged in 2. We were able to follow 2 of the cases throughout their clinical course until they returned to a normal basal metabolism with a complete disappearance of the signs and symptoms. Two of the patients left the hospital prematurely to return to the care of their private physicians and could not be followed further; while 1 patient died from coronary occlusion before intense treatment could be started. The B.M.R. was very low in all cases, and the cholesterol and plasma proteins high in all of them.

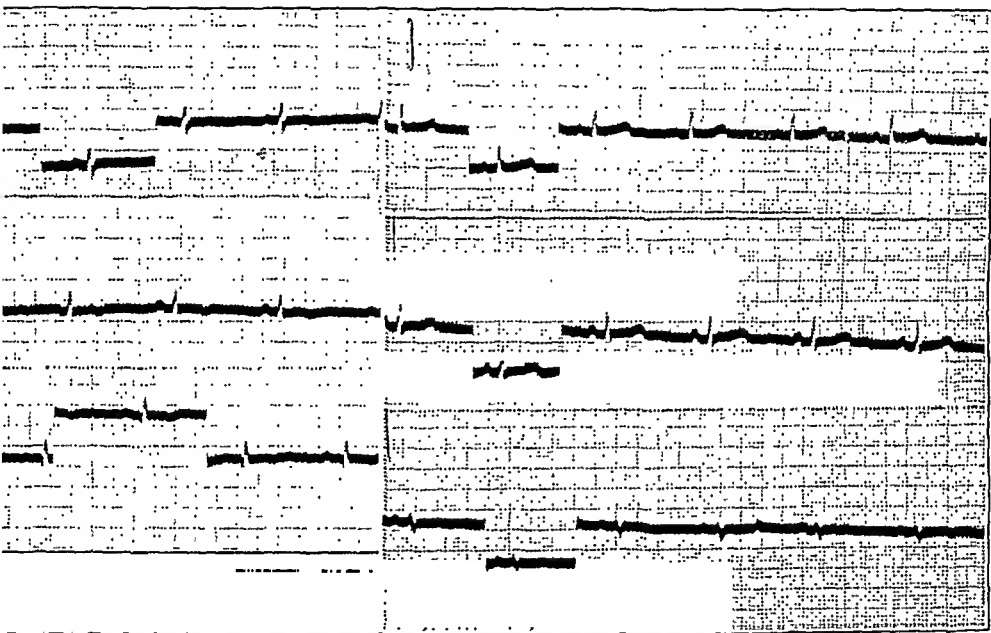


FIG. 7.—The electrocardiogram of Case R. W. before and after treatment with thyroid at the time of high and normal capillary permeability respectively.

In the 2 cases which we were able to follow throughout their clinical course, the permeability curve returned gradually to normal with the increase of the basal metabolic rate and the return of the ECG to normal. One of these cases, which seems to show the clinical course and its relation to the capillary permeability is clearly represented in Table 2 where all pertinent clinical data are entered. The ECG's before the therapy and after return of the basal metabolic rate and permeability curve to normal, are shown in Figure 7. Figure 6 shows the permeability curves as obtained from this patient at the time when the clinical findings as mentioned in Table 2 were present.

Discussion. Finding an abnormally high fluorescence of the skin after the injection of the small-molecular dye fluorescein in cases of myxedema can only be explained by a high capillary permeability. The argument that the skin of the patient with myxedema may have a

TABLE 1.—ESSENTIAL DATA OF PATIENTS UPON ENTRANCE TO THE HOSPITAL

No.	Name	Age	Date of exam.	Circ. time			B.M.R.	Total cholesterol (mg. per 100 cc.)	Total plasma protein (%)	Body weight (lbs.)	ECG	Remarks	Capillary permeability ++ + see Fig. 5
				Arm to lips (sec.)	Arm to arm (sec.)	Leg (sec.)							
1	J. C.	49	1/15/43	—39	24	43	260	7.38	139	P-R prolonged low T waves in all leads, low voltage	No change	1/15/43	++ + see Fig. 5
2	R. S.	65	4/ 2/43	—38	20	36	555	8.95	129	Low voltage, low T waves in all leads	See Fig. 8	1/15/43	++ + see Fig. 5
3	R. W.	35	4/ 7/43	—44	23	61	544	7.87	139	Post. wall infarct	Somewhat low voltage	1/15/43	++ + see Fig. 5
4	G. F.	63	2/19/43	—42	16	35	480	7.90	149	Post. wall infarct	Somewhat low voltage	1/15/43	++ + see Fig. 5
5	M. S.	47	12/31/42	—17	21	50	144	Post. wall infarct	Somewhat low voltage	1/15/43	++ + see Fig. 5

TABLE 2.—R. W., 35 YEARS, WHITE FEMALE

Date of exam.	B.M.R.	Circ. time			Total cholesterol (mg. per 100 cc.)	Total plasma protein (%)	Body weight (lbs.)	Therapy (thyroid in grains)	Remarks	Capillary permeability, see Fig. 6
		Arm to lips (sec.)	Arm to arm (sec.)	Leg (sec.)						
4/ 7/43	—44	23	61	544	7.87	139.5	1 since 10 days	No clinical change	...	++ +
4/27/43	—40	22	55	138.0	1 since 12 days	No marked change	No clinical change	++ +
5/ 2/43	—43	20	40	340	8.16	136.5	1 since 8 days	Improv., normally menstruated for first time since 13 years	Improv., normally menstruated for first time since 13 years	++ +
6/16/43	—26	16	24	150	..	133.0	2 since 7 days	Marked improv.	Marked improv.	Normal
7/ 6/43	—12	17	25	140	..	129.0	2	Marked improv.	Marked improv.	Normal
7/13/43	..	18	30	128.0	2	Perspires for first time	Perspires for first time	Normal
7/17/43	—12	15	23	140	7.20	128.0	2	Normal
9/28/43	—15	14	28	173	6.70	125.0	2 constantly	Normal

higher transparency than normal is disproven by two facts. First, the edema present in the skin tends to decrease the fluorescence since it makes the distance between skin surface and capillary loop wider. Second, direct intracutaneous dye injections into a given pre-set depth did not show any difference in fluorescence in the skin of these patients with myxedema as compared to normals.

After treatment has been instituted, the permeability curve returned rapidly to normal, although no change in the transparency of the skin was noticeable. This return of the permeability curve to normal coincided with marked loss in weight, abundant diuresis, return of the ECG and cholesterol to normal. The plasma proteins returned only later to a basic value.

The amount which diffuses in ultrafiltration through a membrane is directly proportional to the pressure.

Since it is generally agreed that in myxedema the number of capillaries per square millimeter is markedly diminished and since in our cases the diffusion of fluorescein was up to 200% of normal, one can hardly believe that an increase in intracapillary pressure could have caused this increased staining. If this were so and assuming that the number of capillaries per square millimeter were decreased by 50%, one would have to assume that the intracapillary pressure is increased 4 times normal.

This, however, is physiologically impossible.

It seems, therefore, safe to assume that the decrease in capillary permeability under thyroid therapy is the causative factor in the regress of the generalized interstitial edema and the polyserous effusions, which in turn were caused by an abnormally high capillary permeability. It may, therefore, further be assumed that this high capillary permeability is caused by lack of thyroid hormone. There is at present no evidence to indicate that the lack of thyroid hormone causes lack of some other substance which in turn directly causes the change in the capillary endothelium. Such a possibility, however, cannot be excluded. This effect of the thyroid hormone may also explain its diuretic effect in other diseases with a low metabolic rate.

One other possibility should also be mentioned here. Elmby¹ showed that in myxedema the reduction capacity as caused by a lack in ascorbic acid is markedly decreased. Since ascorbic acid has in all probability some influence on capillary permeability this possibility must be kept in mind.

The rapid return of the ECG to normal takes place at the time when the permeability curve returns to normal. This seems to indicate that in many cases, especially in younger patients, the changes are caused much more by the interstitial edema in the heart muscle than by actual changes in the coronary arteries.

Summary. 1. Myxedema tends to form serous effusions, especially in the pericardium, and also a generalized edema. There is marked interstitial edema in the heart muscle.

2. A method using the dye fluorescein is described which, by means of the Dermofluorometer, a photoelectric skin colorimeter, permits the exact estimation of capillary permeability.

3. The values found with this method are in a narrow range for normal individuals (20 cases).

4. Cardiac edema and edema of the lower extremities in cirrhosis of the liver do not go along with an increased capillary permeability, while edema due to undernutrition and severe avitaminosis shows a marked increase in capillary permeability.

5. Five cases of myxedema all showed a marked increase in capillary permeability.

6. With thyroid therapy the permeability rapidly returns to normal, simultaneously with a marked diuresis.

7. The changes in the electrocardiogram before and after treatment are partly attributed to this change in capillary permeability.

8. All cases of myxedema had a prolonged circulation time which returns to normal with effective treatment.

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FACTORS INFLUENCING THE RETURN OF TOLERANCE FOR GLUCOSE IN MIDDLE-AGED OBESE DIABETICS*†

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In recent years there has been renewed emphasis on the mildness of the obese cases of diabetes in contrast to the inherent severity of the

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thin cases. Fetter, Durkin and Dunean⁵ in this country and Schmidt¹² in Europe have been active exponents of this classification of diabetic patients. Draper,² combining anthropologic and clinical studies of a large group of patients with diabetes mellitus, reported an 88% correlation of the mild status of obese "pituitary" cases, and the severity of the thin "pancreatic" type. Kepler³ has found a relationship between the response of patients to protamine zinc insulin therapy and clinical grouping based on the age and weight of patients. He found that the obese adult diabetic is relatively easily controlled with small doses of protamine zinc insulin. Newburgh and Conn¹⁰ have reported many obese patients with hyperglycemia and glycosuria who had a complete return of their carbohydrate tolerance following a reduction in their weight.

The conclusions of a statistical study in this clinic⁷ pointed out that a consideration of diabetic patients, whose diabetes manifested itself after the age of 40 years and who were obese at the onset, must follow a kinetic rather than a static viewpoint. The response of a diabetic to treatment at the onset of his illness gives only a snap-shot of an episode, while the disease goes on for many years. Several factors that alter the course of the disease were pointed out; these factors change the clinical picture so that varying degrees of severity eventually occur in patients with originally mild diabetes. Further studies of these factors form the purpose of this report.

Methods and Results. Fifty-five ambulatory diabetics were selected at random in the Diabetic Clinic of the Long Island College Hospital. All these patients were markedly obese and over the age of 40 years at the onset of their diabetes. Patients whose diabetes was of long duration and who were not seen by a member of the clinic at the onset of the disease were instructed to bring old photographs to substantiate their obesity. Old hospital records were found for many of the long-standing cases yielding data concerning the nature of the onset of the diabetes in some patients 10 to 15 years before this study.

All obese patients were initially put on low-caloric diets until the glycosuria was absent and the patients lost weight. Small additions of carbohydrate-containing foods were later made when the patient's condition improved until the carbohydrate content of the diet was above 180 gm. Patients who were obese at the onset but had lost weight before the time of this study, were usually given diets containing C50, P75, F60. In all cases it was attempted to render the urine free of sugar and to bring the fasting blood sugar to normal levels.

The final estimation of the ability of a patient to regain tolerance for carbohydrate was made, bearing Wilder's cautions¹³ in mind. In this series, no patient had complications known to aggravate the derangement of carbohydrate metabolism, such as infections, liver disease, hyperthyroidism, pregnancy, acromegaly, etc. Since remarkable increases in the glucose tolerance of patients under treatment may come as long as 1 year after therapy is started, the case records of the patients herein reported were rechecked 4 years after the original study. In no case was the first estimation of tolerance found to be wrong.

A modification of the 2-dose oral glucose tolerance test of Exton and Rose¹ was employed. Twenty-five grams of dextrose instead of the usual 50 gm. were given in each dose since all of the patients were known diabetics. Glucose tolerance tests that proved to be normal were repeated (1 exception) with two 50-gm. doses. Capillary blood sugars were estimated by the method of Hagedorn and Jensen⁶ with double determinations.

Glucose tolerance tests were done at varying intervals on each patient. Only the final test is given in this report. The blood sugar after the second dose is considered the best criterion of poor response to glucose, as also recommended by the Mayo group. Only the first obtainable urine reports and fasting blood sugars are given, since the first glucose tolerance tests in some patients were done after treatment was started.

TABLE 1.—PATIENTS WITH DIABETES OF RELATIVELY RECENT ONSET (ALL PATIENTS OBESE AND OVER AGE OF 40 YEARS AT ONSET)

		Before treatment fasting glucose		Exton-Rose test ^{1*} blood glucose			CHO of diet (gm.)	Loss in weight (lb.)	Duration of diabetes	Insulin P.Z. (units)
Sex		Blood (mg. per 100 cc.)	Urine	Fast. (mg. per 100 cc.)	1st ½ hr. (mg. per 100 cc.)	2nd ½ hr. (mg. per 100 cc.)				
Group A. Patients Losing Weight During Treatment (14 Patients)										
M.N.	F	300	++	116	139	157	230	70	R	
F.S.	F	175	+	99	124	143	208	21	R	
W.L.	M	124	++	117	147	154	220	15	R	
M.B.	M	215	++++	92	140	151	200	25+	R	
M.M.	F	224	++	107	153	167	202	23	R	
N.R.	M	130	++	97	132	157	207	21	R	
M.K.	F	207	++++	85	118	124	200	38	1 yr.	
R.H.	F	231	++++	116	194	218	200	24	1 yr.	
A.S.	M	221	++++	121	149	187	167	30+	1 mo.	
M.D.	F	315	++++	105	150	196	200	?	R	
W.	M	172	++	113	145	192	180	38	9 mos.	
M.R.	F	180	+++	129	204	247	180	15	1 mo.	
R.S.	F	350	++++	108	148	179	175	31	1 yr.	
P.D.	M	325	++++	112	162	198	200	28	R	
Group B. Patients Who Lost Weight Before Treatment Was Instituted (13)										
A.H.	F	?	++++	125	143	218	150	60	5 yrs.	
F.R.	F	293	++++	114	167	232	110	27	6 mos.	
J.S.	F	300	++++	122	188	237	150	38	7 mos.	
E.M.	F	?	++++	110	177	222	160	32	3 mos.	
M.T.	F	311	++++	132	215	253	210	36	2 mos.	
A.C.	M	404	++++	160	191	237	165	36	1 mo.	
E.S.	F	386	++++	131	222	247	165	37	3 yrs.	
J.C.	M	401	++++	177	231	263	100—	22	4 yrs.	
M.R.	M	265	++++	120	158	210	180	95	6 mos.	
M.Y.	F	?	++++	119	132	210	220	20	9 mos.	10
J.V.	M	182	++++	96	131	181	210	41	1 yr.	14
C.M.	F	?	++++	134	201	264	213	32	2 yrs.	13
A.P.	F	237	++++	123	182	253	190	33	2 mos.	20
Group C. Patients Who Restricted CHO But Did Not Lose Weight (8 Patients)										
M.B.	F	?	++++	130	187	253	175	5	2 yrs.	
M.R.	M	?	++++	132	170	234	200	0	5 yrs.	
F.U.	F	163	++++	147	159	177	170	0	3 yrs.	
B.B.	M	275	++++	140	155	228	60	0	1 yr.	
F.M.	M	255	++++	152	223	297	150	8	R	
J.B.	F	?	++++	150	184	228	165	5	R	
A.C.	M	300	++++	150	224	259	150	0	R	
F.C.	M	294	++++	178	223	248	100	15	R	

R represents diabetes recently discovered.

* Modified; see text.

The tables given below summarize the results of the study. Table 1 includes patients who were obese and whose hyperglycemia and glycosuria were of relatively recent onset. The sub-groups are divided according to whether they had lost weight or not and also as to whether the loss in weight was due to treatment or neglect. Table 2 includes patients who also were overweight at the onset and who also were older than 40 years; however, the present study of these patients was made a long time after the diabetes was first found. Table 3 tabulates the patients who did not coöperate and who did not adhere to the prescribed diets.

The results will be discussed in light of 4 factors: (1) the weight loss factor; (2) the length of time between the onset of the illness and treatment; (3) the coöperation of the patient; (4) the age of the patient.

The Weight Loss Factor. Newburgh and Conn¹⁰ studied obese middle-age patients who had previously been classified as true diabetics

because of hyperglycemia and glycosuria. When the weights of these patients were reduced by dieting to an ideal level, it was found that glucose tolerance tests became normal. The work of these authors would lead to the belief that most of the obese middle-aged patients who have glycosuria and hyperglycemia fall into this class. In our series of 55 cases, 14 patients (Group A) were all abnormally obese and were older than 40 years. The glycosuria and hyperglycemia had been discovered recently; they all coöperated fairly well in dieting. Only 7 of these patients had normal glucose tolerance tests after varying periods of time, while 7 did not, despite a reduction of their weight to ideal levels.

TABLE 2.—PATIENTS WITH DIABETES OF LONG DURATION (PAST HISTORY REVEALING THAT THEY WERE OBESE AND OVER AGE OF 40 YEARS AT ONSET)

		Before treatment fasting glucose		Exton-Rose test** blood glucose			CHO of diet (gm.)	Loss in weight (lb.)	Duration of diabetes	Insulin P.Z. (units)
Sex		Blood (mg. per 100 cc.)	Urine	Fast. (mg. per 100 cc.)	1st ½ hr. (mg. per 100 cc.)	2nd ½ hr. (mg. per 100 cc.)				
<i>Group D. Patients Remaining Obese for Many Years But Recently Attempting Diabetic Control (7 Patients)</i>										
S.P.	F	392	++++	187	238	217	145	0	8 yrs.	30-0-0
L.M.	F	244	++++	244	316	326	160	?	7 yrs.	0
P.S.	F	?	++++	270	318	448	180	23	8 yrs.	0
S.B.	F	346	++++	232	328	400	60	11	7 yrs.	0
M.C.	F	246	++++	192	224	311	125	5	15 yrs.	15-0-15
R.I.	F	?	++++	190	259	281	110	10	13 yrs.	0
J.A.	F	?	++++	175	221	269	125	0	8 yrs.	25-10-10
<i>Group E. Patients Who Are Thin and Now Attempting Diabetic Control (5 Patients)</i>										
E.H.	F	?	++++	116	128	143	150	36	10 yrs.	5-5-5
A.M.	F	?	++++	132	148	184	150	21	5 yrs.	10-0-10
A.G.	F	?	++++	151	182	267	150	40	10 yrs.	10-0-10
A.K.	F	?	++++	166	195	200	150	50+	13 yrs.	15-15-15
K.J.	F	?	++++	143	200	267	180	92	12 yrs.	10-0-10

* Modified; see text.

Thirteen other patients of the same age group (Group B) gave the history of having been excessively obese relatively recently, but had lost considerable amounts of weight in spite of continued eating before coming to the clinic. Most of these patients did not know they had glycosuria before being examined. Limitation of their food consumption to a low-caloric level was followed by marked improvement of the total carbohydrate tolerance as manifested by the fact that larger diets could be subsequently given with the urines remaining sugar free and the fasting blood sugar returning to a normal level. Despite the previous loss in weight which in many cases was greater than in Group A, none of these patients demonstrated a normal glucose tolerance test after repeated follow-up studies. Even those cases treated with protamine zinc insulin did not have normal glucose tolerance tests after they had become "sugar free."

Group C in Table 1 includes patients similar to those reported by Newburgh and Conn.¹⁰ These patients were indistinguishable from those in Group A as far as history and physical characteristics are concerned. However, they only restricted their carbohydrate intake but did not diminish the total food consumption sufficiently to insure loss of weight. Although the urines of these patients were rapidly

cleared of glucose, the fasting blood sugars never remained at a normal level and the postglucose blood sugars rose excessively. As Newburgh pointed out, one could expect many of these patients to have a complete return of their tolerance for carbohydrate if there had been a reduction of weight.

The different results in these 3 groups of patients demonstrate that loss in weight is an important factor in the obese middle-aged people whose glycosuria and hyperglycemia is of recent onset. It is, however, not the sole factor to be considered, since the manner in which the weight is lost is important. *Dietary restriction* causing weight loss was followed by a remarkable improvement in both clinical responses to treatment as well as laboratory evidence, whereas unlimited eating led to weight loss which was followed by a permanent diminution in glucose tolerance.

It is possible that this difference may be due to the existence of 2 types of obese middle-aged patients with glycosuria and hyperglycemia, one type gaining weight as they overeat, and another group losing weight following excessive indulgence in food. If this be so, there seems to be no way to make a clinical differentiation at the time when both are overweight.

The Length of Time Between Onset and Treatment. In a previous report,⁷ we attempted to point out the differences between adult patients with diabetes of recent onset and those of long duration. The rapid recovery of the ability to assimilate carbohydrate, found in properly treated obese patients whose diabetes was of relatively recent onset, stood out in contrast to the response of obese patients with long-standing diabetes. On the latter there seemed to be a fixation at a low level of the power to assimilate carbohydrates. To illustrate this, the response of 4 obese patients, 2 of recent onset and 2 of long duration, is included. The modified 2-dose glucose tolerance tests are given as well as the carbohydrate content of the diets at the time the tests were made.

Case Studies. **CASE 1. Recent Onset.** L., age 52, male, sales clerk, markedly obese. Glycosuria was discovered during a routine examination 1 week before treatment was started. At the time, the fasting blood sugar was 164 mg. per 100 cc. but no glucose tolerance test had been done.

Length of treatment	Diet	Blood sugars (mg. per 100 cc.)			Urine	
		Fast.	1st ½ hr.	2nd ½ hr.	Fast.	1 hr.
Onset	Unlimited	164	++++	
7 days	C60 for 1 wk.	124	181	243	0	++++
26 days	C220 for 2 wks.	117	147	154	0	0

Total weight lost during this time was 15 pounds.

CASE 2. Recent Onset. M.K., age 49, colored housewife, very obese at onset.

Length of treatment	Diet	Blood sugars (mg. per 100 cc.)			Urine	
		Fast.	1st ½ hr.	2nd ½ hr.	Fast.	1 hr.
Onset	Unlimited	207	257	326	++++	++++
56 days	C180 for 2 wks.	149	203	287	0	++
7 months	C200 for 2 wks.	85	118	124	0	

Total weight lost was 38 pounds.

The recovery of the ability to utilize carbohydrates in these patients was shown by: (1) complete disappearance of the glycosuria; (2) the continued absence of glycosuria despite additions of carbohydrate to the diet; (3) the tendency for the fasting blood sugars to continue to fall to normal; and (4) the glucose tolerance tests approaching the normal standards. In most cases the glycosuria disappeared by the 1st or 2nd week and the fasting blood sugar was decidedly lower by this time although it did not always return to normal level until several months had elapsed. In this same length of time, many obese cases with long-standing diabetes showed none of these characteristics. In fact, many times the urinary sugar and blood sugar *increased* when on restricted diets, as in the next 2 cases.

CASE 3. *Diabetes of 13 Years Duration (plus).* R., age 54, housewife. The patient had been followed in the clinic for 13 years. Her old records showed that by dieting she could readily clear up her glycosuria, however, she was a "chronic cheater" and remained obese. She had refused insulin for all these years despite continued glycosuria. The present study was performed when she was hospitalized for study of a recent precordial pain and for dietary regulation. In the hospital, hypertensive heart disease was found; the EKG was normal. A diet containing 1130 calories was given for 3 weeks while she was studied; no insulin was used. "Traeces" of sugar were usually present in her urine. The fasting blood sugars tended to rise and more sugar appeared in the urine during this time despite a loss of weight. The following tests were performed while the patient was in the hospital; the tests which were performed while she was treated in the clinic are not included because of the probability that she did not rigidly adhere to her diet.

Length of treatment	Diet	Blood sugars (mg. per 100 cc.)			Urine
		Fast.	1st ½ hr.	2nd ½ hr.	
Onset	C135 P60 F65	160	215	263	++
18 days	C110 P60 F50	192	259	281	+++

Total loss of 11 pounds in 18 days.

The study was discontinued so that insulin could be started. She subsequently received insulin 20-10-10 to regulate the diabetes.

CASE 4. *Diabetes of 10 Years Duration (plus).* J., age 55, housewife. This patient was a known diabetic for 7 years. She remained obese, eating large quantities of candy, cake, etc., and did not pay attention to the pruritis, polydipsia, etc. She entered the hospital because of a severe neuropathy. In the hospital she was kept on a 900-calorie diet for over a week. During this time, the urine continued to give a brick red "Benedict's" reduction and the fasting blood sugars rose from 314 to 322 mg. per 100 cc. despite a loss of 4 pounds in weight.

Length of treatment	Diet	Insulin	Blood sugars (mg. per 100 cc.)			Urine
			Fast.	1st ½ hr.	2nd ½ hr.	
Onset	"Restricted"	None	314	N.D.	N.D.	++++
9 days	C60-900 cal.	None	322	340	354	++++
7 days more	C125-1400 cal.	30 P.Z.I.	266	309	341	++++
4 days more	C125-1400 cal.	45 P.Z.I.	202	231	326	++++
2 months	C125-1400 cal.	25-10-10	175	221	269	+

There was a total loss of 17 pounds during this period.

In this series of 55 obese diabetics, there were 7 patients (Group D in Table 2) who had remained markedly obese during many years because

of neglected treatment. Some had been given "free diets" with "insulin to cover." All of these patients were persuaded to attempt diabetic control with low-caloric diets; none of these patients demonstrated an ability to regain carbohydrate tolerance after losing weight. Four of these 7 patients were hospitalized; the course in the hospital corroborated the experience in the clinic. The 2-dose glucose tolerance tests after they had been on low-caloric diets were uniformly bad. The fasting blood sugar values were always higher than normal, and the postglucose responses were markedly exaggerated. To 5 of these 7 patients, the inability to reduce the glycosuria with diet alone came as a surprise, since they had been able to do so in the past. Such histories suggested that the persistent and long-standing neglect in restricting the caloric intake led to a progression in the severity of the diabetes ending in a permanent depression of the glucose tolerance.

The fact that both the length of time a patient has had improper treatment as well as the lack of adequate weight reduction seem to impair the ability of middle-aged obese diabetics to regain tolerance for carbohydrate raises the question as to which of the two is more important. In the diabetic clinic we have followed many patients similar to those in Group A in whom there has been no return of glycosuria or hyperglycemia after 8 years; this coincides with Newburgh's findings. However, a study of the 5 patients in Group E (Table 2) was informative. These patients had been markedly obese at the onset of their diabetes many years before the present study. Most of them gave a typical history of having followed a restricted dietary regimen for variable periods of time after the diagnosis had been made. However, after they had lost weight they became more careless in dieting, leading to a return of a severe diabetic state. For the most part, low-caloric diets given during the present study decreased the glycosuria and lowered the fasting blood sugar. Insulin had to be given early in the course of treatment because of obvious difficulty in keeping such patients on low-caloric regimen. A comparison of the end-results of treatment of these "thin patients with long-standing diabetes" (Group E) with "thin patients with diabetes of recent onset" (Group B) is interesting. All of the former had a definitely lowered tolerance for carbohydrate than the latter, as evidenced by the fact that all of the former needed insulin and the diets could not be raised to as high levels without a return of glycosuria. It was interesting to note, however, that the 2-dose glucose tolerance tests (which were performed after unmodified insulin had been given on the previous day) were of "moderate severe degree" in contrast to the tests obtained in "obese patients with long-standing diabetes (Group D) which were exceedingly bad." These findings suggest that prolonged neglect in the treatment of the mild adult form of diabetes leads, after a period of time, to a restriction in the amount of carbohydrate that the patient can consume, but that the patient's ability to manage glucose efficiently is not as markedly impaired by this factor as it is by lack of an adequate reduction in weight.

It must be pointed out that most of the patients reported here as

having "long-standing diabetes" had the diagnosis originally made over 7 years before the present study. Because of the small number of cases reported here, an adequate estimation of the length of time that it takes for the diabetes to progress cannot be made.

The Coöperation of the Patient. In a recent study, Colwell¹ claimed that diabetes mellitus became progressively more severe in all patients, and that the rate of progression was more or less determined at birth. He found in his large series of patients that treatment altered the natural course of the disease for only a few years, after which the progressiveness again manifested itself. This is in contrast to the views of many older clinicians, such as Naunyn, who found that diabetes could be checked by dietary management. In this study, it was obvious that coöperation on the part of a patient in following dietary prescriptions was a very important factor in the eventual results. For instance, when separating the patients in Group A from those in Group C, the chief criteria were that the former coöperated strictly and lost weight, whereas the patients in the latter group restricted their food intake sufficiently to become aglycosuric, but not to the extent that they could lose weight. Differences in coöperation are stressed when non-diabetic obese patients are studied, but are not emphasized in diabetic literature. However, the extreme importance of this factor in diabetics was shown by the fact that careful adherence to the low-caloric regimen by patients in Group A was rewarded by a return to normal carbohydrate tolerance in at least 50% of the cases, and by the fact that none had glycosuria after the oral administration of 50 to 100 gm. of glucose. Patients in Group C did not show such excellent results. Their fasting blood sugars remained elevated and although the postabsorptive urine contained no glucose, most had glycosuria after the administration of two 25-gm. doses of glucose.

TABLE 3.—PATIENTS WHO ARE OBESE AND OVER AGE OF 40 YEARS (NOT COÖPERATING WITH DIETING)

		Before treatment fasting glucose		Exton-Rose test** blood glucose			CHO of diet (gm.)	Loss in weight (lb.)	Duration of diabetes	Insulin P.Z. (units)
Sex		Blood (mg. per 100 cc.)	Urine	Fast. (mg. per 100 cc.)	1st ½ hr. (mg. per 100 cc.)	2nd ½ hr. (mg. per 100 cc.)				
Group F. Cases Similar to Group A (3 Patients)										
G.P.	F	320	++++	222	287	324	60?	14†	1 yr.	0
B.F.	F	254	++++	219	281	336	200?	19†	½ yr.	0
R.N.	M	?	++++	150	255	353	215	0	½ yr.	40-0-0
Group G. Cases Similar to Group E (5 Patients)										
A.C.	F	?	++++	170	206	250	165	30	14 yrs.	20-0-0
M.M.	F	325	++++	204	242	285	180	50	11 yrs.	22-0-0
F.M.	F	320	++++	197	262	300	150	40	12 yrs.	0
I.N.	F	?	++++	286	298	348	180	40	7 yrs.	15-0-10
C.M.	F	122	++	221	314	385	170	58	9 yrs.	0

* Modified; see text.

† Gain of weight.

The differences in the results just mentioned were due to relatively minor infringements in dieting. An additional 8 patients did not restrict their food intake at all. Three of these (Group F, Table 3) should have had results similar to Group A or Group C since they were also obese, over the age of 40 years at onset and the diabetes was dis-

covered shortly before this study. However, because of constant misbehavior they had very high fasting and postglucose blood sugars. All 3 were subsequently given protamine zinc insulin, which did not clear up the glycosuria. Similar results were found by Fetter, Durkin and Duncan⁵ who pointed out that obese diabetics cannot be controlled by insulin alone when they do not restrict their diets at all. The patients later become the "obese cases with long-standing diabetes" who after 6 or 7 years do not have a return of carbohydrate tolerance even when dieting strictly.

Another interesting contrast was presented by the 5 patients in Group G in Table 3. These patients had lost tremendous amounts of weight because of lack of proper dieting over many years. The fact that their weight had been reduced to normal or below did not alter the necessity for dieting. The high-fasting and postglucose blood sugars were reflections of the patient's lack of adherence to a proper diet. It is our impression that these patients with diabetes neglected over many years feel better when their blood sugars are allowed to remain at a higher level; we do not attempt to obtain rigid chemical control in the clinical management of such patients. For this reason, it is emphasized that the results found in Group G are included merely for comparison with those obtained in Group E, since both had similar clinical backgrounds, but they differed in the degree of coöperation in dieting.

The Age Factor. Statistical studies have shown that incidence of obesity becomes the most important factor in the etiology of diabetes at the period of life that may be called "the beginning of middle age." As was demonstrated above, the presence of obesity is the most important factor influencing the progression of the disease. However, the age factor cannot be overlooked. Colwell's¹ studies show that the rate of progression of diabetes is slower when the disease manifests itself clinically at a later age. Thus the earlier the age of onset, the severer is the future course of the diabetes. In this clinic, the onset of the diabetes at 40 years of age is selected as the dividing line between so called "middle-aged obese" and young diabetics. Others have chosen 35 years to 45 years as the dividing age of onset. One of the chief criticisms leveled against the grouping of diabetics according to age and weight is that there are too many exceptions when any one single age level is chosen. Against these objections are the many advantages of making these groupings so that early diagnosis, definitive treatment, and specific aims in therapy can be emphasized as has been done above. The age of onset was selected as 40 years because we have seen many obese patients between the age of 35 years and 40 years (particularly women whose diabetes was found during pregnancy) whose deranged carbohydrate metabolism rapidly became worse even with treatment within a period of 3 to 5 years. In contrast, we have seen exceptionally few obese diabetics whose disease seemed to manifest itself after the age of 40 years who have not had a mild subsequent course. In fact, in patients who coöperated well, the disease became milder with time.

Conclusions. Obese patients who are over 40 years of age when they first have glycosuria and hyperglycemia should be treated by rigid dietary restriction aiming for reduction of weight, for disappearance of glycosuria, and for a physiologic blood sugar level. When treated in this manner, there may be a remarkable return of tolerance for carbohydrate. Careful coöperation in following the dietary prescription on the part of the patient is needed to obtain these results.

The diagnosis of diabetes must be made early in such patients, because if weight is lost by neglect in treatment, the ability to regain tolerance for carbohydrate becomes impaired. Response to treatment in such patients is still good, particularly when protamine zinc insulin is used.

Obese patients who neglect treatment for many years and remain obese, lose the ability to regain their tolerance. They become difficult to treat. Diet therapy in these patients seems to be of little value. Their blood sugar levels remain elevated even with insulin. Those patients who neglect treatment for many years and who eventually lose weight also show diminished tolerance, but the management of the deranged glucose economy is less difficult than in those who remained obese.

Summary. 1. Glycosuria and hyperglycemia occurring in obese patients after the age of 40 years represent a temporary decrease in the patient's tolerance for carbohydrate.

2. Prompt treatment consisting of weight reduction by means of low-calorie regimens can lead to a remarkable return of the patient's tolerance for glucose. In some cases, the deranged carbohydrate tolerance becomes normal.

3. A kinetic viewpoint must be maintained when viewing the course of these cases. The most important factors diminishing the ability of a patient to regain carbohydrate tolerance are: (a) the lack of proper weight reduction; (b) delay in treating the patient over a period of years; (c) poor coöperation on the part of the patient in following a dietary regimen which aims at effecting a weight loss; (d) the onset of the diabetes at an early age.

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THE RELATIONSHIP BETWEEN HORMONAL ABNORMALITIES AND ACCIDENTS OF LATE PREGNANCY IN DIABETIC WOMEN*

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PREVIOUSLY reported studies from this laboratory of hormonal changes during pregnancy^{1-5,7} have been primarily concerned with toxemia and have indicated that preëclampsia and eclampsia in diabetic as in non-diabetic women are characteristically preceded and accompanied by a typical imbalance as revealed by aberrations from the normal in the measurable hormones or hormonal products of the blood and urine. An abnormal rise in the chorionic gonadotropin (C.G., A.P.L., prolan) of the serum 4 to 8 weeks prior to any clinical signs is the most easily detected of these changes, but has been a less consistent finding than urinary evidence of a changed metabolism of the placental steroids involving a progressive deficiency of estrogen and progesterin and culminating in more rapid destruction of estrogen.

In our early studies of diabetic pregnancies, there was some indication that the same hormonal abnormality which typifies preëclampsia and eclampsia also pertained in those accidents of late pregnancy involving death of the offspring, a frequent occurrence in diabetic women. As a result of our findings and at our instigation, administration of estrogenic and progestational substances to diabetic patients showing an abnormal rise in serum C.G. has been given a rather extensive trial at the George F. Baker Clinic of the New England Deaconess Hospital. Articles from this laboratory^{1,2,3,5} have covered our studies of 33 of the cases reported independently from that clinic.¹¹⁻¹⁴ The present investigation, conducted entirely on diabetic women to whom no hormones were administered, was undertaken primarily with the purpose of obtaining more complete data concerning the consistency of the relationship between hormonal abnormalities and the development of later clinical mishaps, particularly those involving fetal or neonatal death. We were also interested in following the metabolism of the placental steroids from an earlier period of gestation than has previously been studied except in normal pregnancy.

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Material and Methods. In 16 pregnant women with diabetes, serum C.G. was measured at 1- to 2-week intervals starting between the 16th and 29th weeks. In 8 of them, the metabolism of the placental steroids was also studied by repeated quantitative analyses of 24-hour specimens of urine for estrogen metabolites. The same methods of analysis of serum² and urine^{8,9} were used as in previous studies except that estrone and α estradiol fractions were separated by a micro-modification of the Girard method and assayed individually rather than depending upon the difference in activity before and after treatment by semicarbazide for the estimation of estrone. Urinary pregnanediol was not measured, since previous findings indicated that the excretion of this compound runs roughly parallel to that of estriol, and gives no information about the metabolism of progestin that is not more adequately provided by determining the amount and partition of the separated urinary estrogens and the amount of additional potency that may be derived from urine by hydrogenation with zinc and HCl.

TABLE 1.—CLINICAL NOTES ON PREVIOUS PREGNANCIES AND DIABETES

Name	Age	Parity	Date of this pregnancy	History of previous pregnancies	Diabetes first diagnosed*	Daily insulin requirements
<i>Cases With Abnormal Elevation of Serum Chorionic Gonadotropin</i>						
R. S.	23	II	1942-43	1 stillborn 1939	Fol. 1st dely. 1939	72 U. Prot. Zn 25 U. reg.
E. C.	38	III	1941-42	2 stillborns 1930, 1931	1923	32 U. Prot. Zn 20 U. reg.
E. H.	30	I	1941-42	This preg. 26th week	12 U. Prot. Zn
J. L.	27	I	1941	This preg. 23rd week	None
F. L.	19	I	1940-41	1938	90 U. reg.
E. S.	25	I	1942-43	1929	35-40 U. Prot. Zn 12 U. reg.
S. L.	26	I	1941-42	1931	60-80 U. reg.
<i>Cases With Normal Serum Chorionic Gonadotropin</i>						
C. H.	25	I	1942	1939	80-120 U. reg.
M. M.	36	II	1942	1 stillborn 1932	1933	30-45 U. reg.
E. D.	21	II	1941	1 nor. 1939	1938	70 U. Prot. Zn 20 U. reg.
E. B.	25	II	1941	1 nor. 1939	Last preg. 1939	12-28 U. reg.
L. S.	39	X	1942	8 nor., 1 misc. 1925-1939	This preg. 1st visit†	16 U. Prot. Zn
D. H.	23	I	1942-43	1938	52 U. Prot. Zn 20 U. reg.
E. F.	23	I	1941-42	1940	52-72 U. Prot. Zn
A. P.	29	V	1940-41	4 nor. 1930-38	This preg. 28th week	None
I. S.	37	IV	1941-42	3 nor. 1924-1936	This preg. 23rd week	16-40 U. reg.

* Glycosuria with or without symptoms, a glucose tolerance curve of the diabetic type and a fasting blood sugar of 140 mg./100 cc. or over.

† Excessive thirst since 1940.

Serum Chorionic Gonadotropin and Later Accidents. Clinical data in relation to the values for serum C.G. are summarized in Tables 1 and 2, and indicate that neither the duration nor the severity of the diabetes are factors in an abnormal elevation of serum C.G. Furthermore, the incidence of toxemia and the size or condition of the offspring appear to be unrelated to the history or severity of the disease. All of the

patients were seen at weekly intervals throughout pregnancy by one of us (D.H.) for careful control of the diabetes.

TABLE 2.—CLINICAL NOTES ON THE PREGNANCIES STUDIED

Name	Late pregnancy toxemia*					Delivery		Condition of offspring	
	Alb.	Hyp.	Ed.	S.S.	Conv.	Week of gestation	Type	Weight	
<i>Cases With Abnormal Elevation of Serum Chorionic Gonadotropin</i>									
R. S.	—	—	—	—	—	40	Spont.	Macerated	Stillborn; died 3 wks. pre-part.
E. C.	+	—	+	—	—	34	Cesarean	6 lb. 11 oz.	Intraut. asphyxia, cyanosis, survived
E. H.	+	—	+	—	—	39	Spont.	8 lb.	Normal
J. L.	+	—	+	—	—	40	Spont.	9 lb. 4 oz.	Normal
F. L.	+	+	+	+	+	39	Induced	8 lb. 3 oz.	Normal
E. S.	+	+	+	—	—	35	Spont.	Macerated	Stillborn; died 2 wks. pre-part.
S. L.	+	+	+	+	—	35½	Induced	5 lb. 11 oz.	Died 36 hrs. post-part., left subarachnoid hemorrhage
<i>Cases With Normal Serum Chorionic Gonadotropin</i>									
C. H.	+	—	+	—	—	39	Induced	6 lb. 4 oz.	Normal
M. M.	+	+	+	—	—	37	Spont.	6 lb. 12 oz.	Stillborn, intraut. asphyxia; died 3 days pre-part.
E. D.	—	—	—	—	—	35	Spont.	7 lb. 8 oz.	Normal
E. B.	—	—	—	—	—	36½	Spont.	8 lb. 4 oz.	Died 15 hrs. post-part., intraut. pneumonia, adrenal hemorrhage
L. S.	—	—	—	—	—	32	Spont.	Macerated	Stillborn; died 1 wk. pre-partum
D. H.	—	—	—	—	—	44	Spont.	Macerated	Stillborn; died 6 wks. pre-partum
E. F.	—	—	—	—	—	39½	Spont.	6 lb. 14 oz.	Normal
A. P.	—	—	—	—	—	40	Spont.	11 lb. 4 oz.	Normal
I. S.	—	—	—	—	—	40	Spont.	8 lb. 14 oz.	Normal

* The abbreviations in the subheadings stand for the following: alb. = albuminuria; hyp. = hypertension; ed. = abnormal gain in weight or visible edema; S.S. = subjective symptoms; conv. = convulsions.

An Early Elevation of Serum C.G. This abnormality was detected in 7 of the 16 patients between the 25th and 33rd weeks of gestation.* Six of these developed toxemia of varying degrees of severity at 31 to 37 weeks and the 7th (R.S.) had intrauterine death at 37 weeks with no other clinical abnormality. In 3, toxic signs were mild, being limited to albuminuria and edema. One of these (E.C.) was delivered by cesarean section during the 34th week because of failure to control increasing albuminuria by conservative measures together with a history of stillbirth in each of 2 previous pregnancies. The 6 lb. 11 oz. baby was cyanotic for several days but survived. The other 2 had normal deliveries at term of rather large but perfectly healthy infants, one (E.H.'s) weighing 8 lb. and the other (J.L.'s) 9 lb. 4 oz. In both, the mild toxic signs disappeared during the last week of pregnancy following a lowering of serum C.G. to normal levels. In other words, both the hormonal and clinical abnormality appeared to be self-corrected.

Of the other 3 patients with an early elevation of serum C.G., one (F.L.) had eclampsia during the 39th week with delivery, after artificial rupture of the membranes, of a normal 8 lb. 3 oz. infant. Two had preëclamptic toxemia: one (E.S.) with a blood pressure of 150:90,

* Our criterion for normal serum C.G. is based upon the analyses of 235 serums from 67 normal pregnancies. In 39 of these, including 10 complicated by diabetes, repeated analyses were performed and in no case was an elevation above 100 r.u. per 100 cc. found between the 20th and 36th weeks.⁵

albuminuria (3 gm. in 24 hours) and edema at 31 weeks and intrauterine death at 33 weeks; in the other (S.L.) labor was induced at 35½ weeks because of blurring of vision, hypertension (180/110) and albuminuria (7 to 8 gm. in 24 hours). The 5 lb. 11 oz. infant died 36 hours after birth.

Normal Serum C.G. Of the 9 patients in whom serum C.G. remained normal between the 25th and 36th weeks, 2 developed toxemia. In one (C.H.) toxic signs were limited to slight albuminuria (0.2 to 0.3 gm. in 24 hours) between the 30th week and term and edema of the ankles at term, when labor was induced and a normal 6 lb. 4 oz. infant delivered. The other (M.M.) had slight albuminuria (0.2 to 0.3 gm. in 24 hours), edema and hypertension (highest reading 150/82) starting at the 31st week. During the 37th week intrauterine death occurred. Two of the 9 with normal serum C.G. had pyelitis and spontaneous premature delivery at 35 and 36½ weeks, respectively. Both of the infants were large for this period of gestation, 7 lb. 8 oz. and 8 lb. 4 oz. The 35-week-old infant (E.D.'s) was healthy and survived, but the other (E.B.'s) died 15 hours after birth, the diagnosis after autopsy being intrauterine pneumonia and adrenal hemorrhage. There were 2 other fetal deaths in this group with normal serum C.G. One (L.S.) had intermittent uterine bleeding starting during the 25th week. Intrauterine death occurred during the 31st week. The other (D.H.) had a normal pregnancy up to the 38th week, when intrauterine death occurred. The other 3 cases of this group (E.F., A.P. and I.S.) had normal pregnancies throughout with full-term delivery of healthy infants weighing 6 lb. 14 oz., 11 lb. 3 oz. and 8 lb. 14 oz., respectively.

From this study, together with those previously reported,^{2,4} it is safe to conclude that the finding of a rise in serum C.G. between the 25th and 35th weeks in either diabetic or non-diabetic women warrants the prediction of later trouble, although it gives no indication of the type or severity of the trouble, which may be only mild (and occasionally self-corrected) toxemia, preëclampsia, eclampsia or death of the offspring. However, from the data presented it is obvious that later mishaps may occur without any premonitory rise in serum C.G. Although a fairly consistent relationship is again demonstrated between such a rise and toxemia of varying degrees of severity, the incidence of fetal or neonatal death was no higher in this group than in those in whom no elevation occurred. Normal levels of serum C.G. from the 25th to 35th weeks in diabetic patients, therefore, provide no assurance that the rest of pregnancy will be uneventful, particularly as regards the prognosis for the fetus.

Metabolism of the Placental Steroids and Later Accidents. Although elevated serum C.G. has not, in our experience, been an absolutely consistent finding in preëclampsia and eclampsia,^{2,4} none of 23 previously reported cases of this disease^{4,6} in which repeated complete urinary analyses were done failed to give evidence of a typical abnormality in the metabolism of the placental steroids, despite the fact that in 6 of them serum C.G. was normal. We were particularly interested in determining whether or not death of the offspring was also more

closely related to deficiency of estrogen and progesterin than to high serum C.G. levels. In 8 of the present group of 16 patients, urinary analyses were performed for the separated estrogens and for the increased potency produced by hydrogenation with zinc and HCl. The pregnancies of 4 (R.S., E.S., M.M. and D.H.) terminated in death of the offspring, and that of a 5th (E.C.) in cesarean delivery at 34 weeks of a viable but cyanotic infant that barely survived. In all 5, evidence of a deficiency of placental steroids preceded the accident, although in 2 (M.M. and D.H.) repeated analyses of serum revealed normal levels of C.G. The failure to find high serum C.G. in some cases of fetal or neonatal death, therefore, does not exclude the possibility that the deranged metabolism of the placental steroids which characterizes toxemia of late pregnancy may not pertain.

It would also appear that if this deranged metabolism is in any way etiologically concerned in these accidents, it may take its toll either from the maternal or fetal organism but not necessarily from both. In 7 of the 8 patients whose urinary estrogens were studied, this abnormality was found. Two of them (R.S. and D.H.) had intrauterine death with no toxic signs. Two (J.L. and F.L.) had toxemia with normal offspring, despite the development in one (F.L.) of full-blown eclampsia at 39 weeks. In the other (J.L.), mild toxic signs disappeared during the 38th week coincident with a self-correction of the endocrine abnormality. Only 3 of the 7 with abnormal metabolism of the placental steroids had both toxemia and fetal abnormalities (E.C., E.S. and M.M.). E.F. was the only one of this group in whom the urinary findings reflected normal steroid metabolism, and she alone had both a normal pregnancy and a healthy child.

TABLE 3.—SUMMARY OF HORMONAL FINDINGS IN RELATION TO OBSTETRICAL OUTCOME

Name	Serum C.G.		Steroid metabolism		Obstetrical notes	
	Specs.	Results	Specs.	Results	Mother	Offspring
R. S.	9	High	9	Abnormal	Normal	I.U.* death
E. C.	9	High	3	Abnormal	Mild toxemia	Cyanotic but survived
E. H.	5	High-s.c.†	Mild toxemia	Normal
J. L.	7	High-s.c.†	5	Abn.-s.c.†	Mild toxemia	Normal
F. L.	6	High	4	Abnormal	Eclampsia	Normal
E. S.	11	High	10	Abnormal	Preëclampsia	I.U.* death
S. L.	9	High	Preëclampsia	N.N.‡ death
C. H.	5	Normal	Mild toxemia	Normal
M. M.	4	Normal	2	Abnormal	Preëclampsia	I.U.* death
E. D.	6	Normal	Prem. dely.	Normal
E. B.	5	Normal	Prem. dely.	N.N.‡ death
L. S.	3	Normal	Prem. dely.	I.U.* death
D. H.	9	Normal	9	Abnormal	Normal	I.U.* death
E. F.	6	Normal	3	Normal	Normal	Normal
A. P.	8	Normal	Normal	Normal
I. S.	8	Normal	Normal	Normal

* I.U. = intrauterine.

† s.c. = self-corrected.

‡ N.N. = neo-natal.

Table 3 summarizes hormonal findings in relation to clinical outcome in all cases. The detailed results in 5 of the 8 whose urines were

analyzed for metabolites of estrogen will not be reported here, since collections were not begun until after the 31st week. The results, therefore, add nothing to those already published except that fetal and neonatal death, whether or not accompanied by toxemia, appears to be closely associated with the same abnormality of the placental steroids which characterizes preëclampsia and eclampsia.

In Figures 1 and 2 are presented the most pertinent findings in the other 3 patients whose urines were analyzed, specimens having been collected from an earlier period of gestation than has before been studied in either diabetic or non-diabetic women in whom toxemia or death of the offspring occurred.

Explanation of Charts. T_0 , i. e., total urinary estrogen, expressed in terms of estrone equivalents (Fig. 1) represents the sum of the estrogenic activities found in the estradiol plus estrone plus estriol fractions. In general it may be said that a rise in T_0 is due to an increase in all 3 fractions but is accompanied by a change in the partition of the estrogenic activity between these fractions which points to an increased rate of conversion of estradiol to estrone to estriol and hence to greater secretion of progesterin, whose presence facilitates this conversion. Conversely, a drop in T_0 is characteristically associated with a changed partition of the total activity between the 3 fractions which indicates decreased conversion of the estrogens and hence withdrawal or deficiency of progesterin.*

The amount of estrogenic activity produced by Zn-HCl hydrolysis of the urine, over and above that accounted for by estrogens excreted as such, is termed "unaccounted for" T_0 . The exact derivation of this activity remains to be established, although the weight of evidence points to non-estrogenic excretory products resulting from oxidation of estrogens *in vivo*. Its 24-hour value, as related to that of total estrogens excreted as such ("unaccounted for" T_{24} to T_0 ratio—Figure 2), is interpreted as providing a gauge of the rate of destruction of estrogens in the body and consequently of secretion of progesterin, since progesterin reduces destruction of estrogens in addition to facilitating their conversion.*

The heavy solid lines in Figures 1 and 2 are composite curves based on published data from normal pregnancies.^{4,10} The double line represents the findings in one of the normal pregnancies in which repeated complete urinary analyses were started earlier than in the rest, namely, at 16 weeks. Separated estrogens in this case have been published.³

The 3 patients chosen for this study (R.S., E.S. and D.H.) were young, with fairly severe diabetes of 3 to 13 years' duration (see Table 1). In all, pregnancy terminated in intrauterine death, 2 with (R.S. and E.S.) and 1 without (D.H.) a preceding rise in serum C.G. E.S., the only one in whom there were any toxic signs, was placed under hospital care for preëclampsia at 31 weeks. Two weeks later the fetal heart could not be heard and a macerated fetus was delivered during the 35th week. In the other 2 patients intrauterine death occurred, without any other clinical signs of abnormality, at the end of the 37th week. Stillbirth came 3 and 6 weeks later.

The results of only the first urinalysis after death of the fetus are included in the charts. In each case this specimen was collected within a few days of the accident. Thereafter the excretion of estrogens dropped precipitously, but, even in D.H., who carried the dead pregnancy for 6 weeks, never reached non-pregnant levels until after delivery of the macerated fetus and placenta.

* For a more complete explanation of these interpretations of our findings, the reader is referred to previous publications from this laboratory.^{1,3-6,8,10}

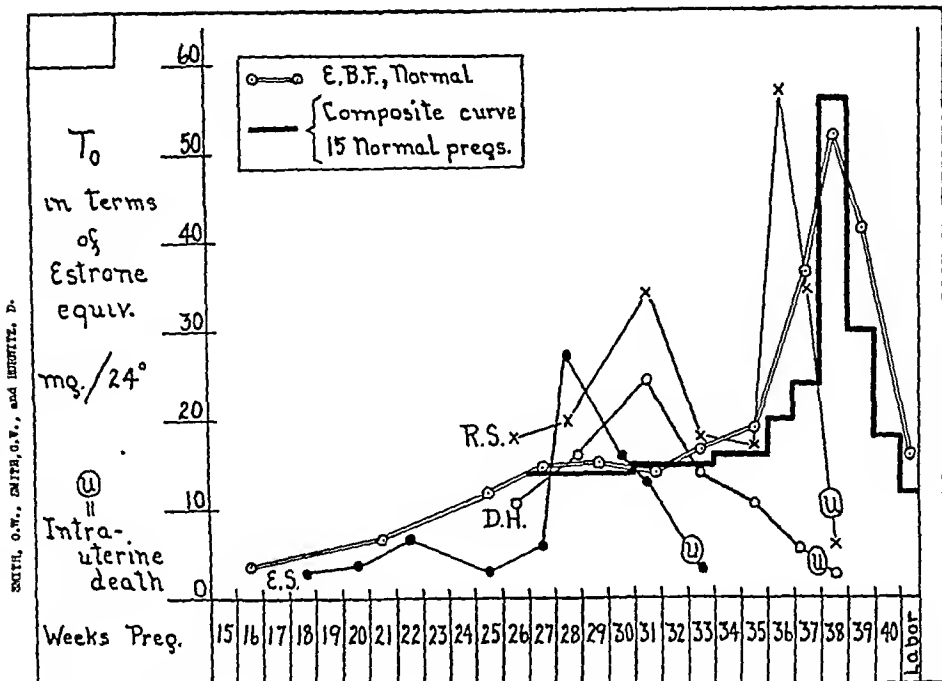


FIG. 1.—Rate of estrogen excretion. Total estrogenic activity (T_0 = estradiol + estrone + estriol) of repeated specimens of urine from 3 pregnant women prior to intra-uterine death compared with normal curves of total excretion of estrogens.

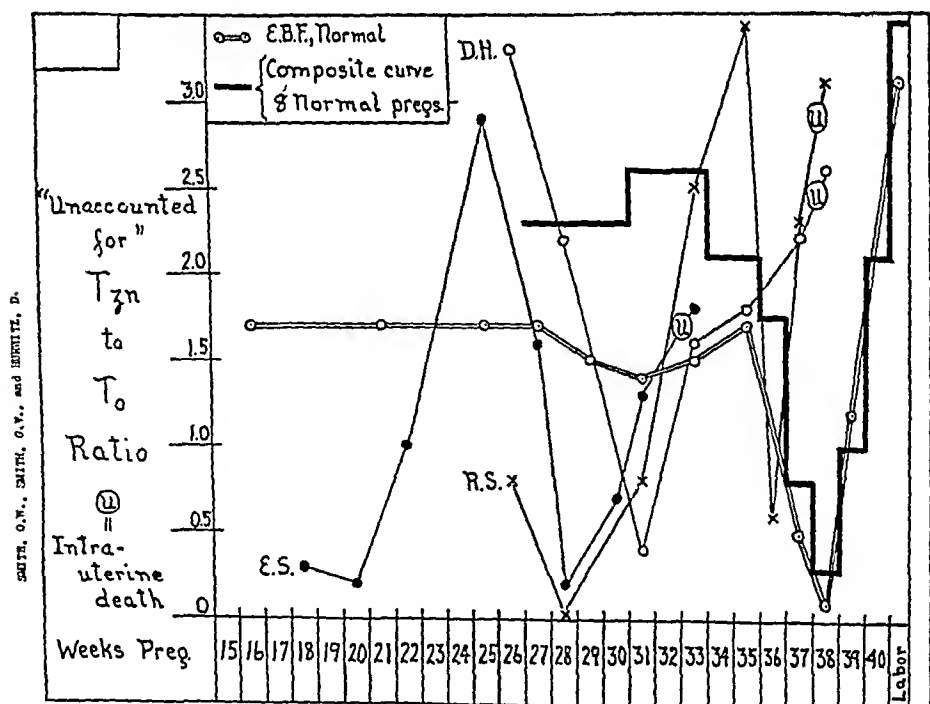


FIG. 2.—Rate of estrogen degradation. Ratio of increased activity produced by hydrogenation ("unaccounted for" T_{zn}) to total excretion of active estrogens in repeated specimens of urine from 3 pregnant women prior to intrauterine death compared with ratios based on normal pregnancies.

In each case, intrauterine death occurred at a time when the urinalyses reflected a markedly downward trend in the rate of conversion of estrogen together with a striking increase in its rate of destruction; in other words, according to our interpretation, a progressive deficiency of both estrogen and progesterin. Evidence for this shift in steroid metabolism has been a consistent finding before and during the development of preëclampsia and eclampsia. It is entirely similar to the hormonal situation which immediately precedes normal labor and delivery.

In these 3 patients, moreover, all of whom were followed 12 to 15 weeks before intrauterine death, an even earlier deviation from the normal was discovered. In each, between the 25th and 31st weeks, a sudden increase in the rate of conversion (as indicated by increased excretion of all 3 estrogens, particularly estrone and estriol) and decrease in the rate of destruction (as indicated by a striking drop in the amount "unaccounted for" T_{zn}) were observed. This situation, presumably reflecting increased placental secretion of both estrogen and progesterin, does not begin to develop to such a marked extent in normal pregnancy until around the 36th week. In fact, in none of the normal controls did the ratio of "unaccounted for" T_{zn} to T_o activity fall below one prior to the 35th week. In other words, the analogy between the hormonal changes which precede the development of accidents of late pregnancy and those which precede labor started earlier than has before been demonstrated and included evidence for the markedly increased rate of production and metabolic conversion of the placental steroids, which normally reaches a peak 2 to 3 weeks before labor, as well as the subsequent withdrawal phenomenon. The whole picture, therefore, indicates premature changes in the placenta with the development of toxemia or damage to the fetus or both at the time when premature labor and delivery might be expected.

In D.H., only one such period of maximum conversion and minimum destruction of the estrogens was detected, at 31 weeks; this being followed by urinary evidence of a progressive drop in the rate of conversion and rise in the rate of destruction for 6 weeks prior to fetal death. In R.S., the same pattern was followed through the 35th week. During the 36th week, however, a striking increase in total excretion of estrogen together with a precipitous drop in "unaccounted for" T_{zn} activity pointed to a spurt in the production of the placental steroids. It is interesting that the fetus was thought to be growing more rapidly and to be more active during this time. This episode, which suggests an attempt at self-correction of the hormonal abnormality, was followed by a sudden change in the opposite direction and death of the offspring. In E.S. also 2 cycles of excretion were detected. Although total estrogens were not high between the 18th and 22nd weeks, their partition and the very low values for "unaccounted for" T_{zn} indicated an unusually rapid rate of conversion of estradiol to estrone to estriol together with very little breakdown of estrogen. A high ratio of progesterin to estrogen for this period of gestation is suggested. This situation was followed by evidence for a period of progesterin withdrawal which was interrupted by a temporary increase in total estrogen and decrease in "unaccounted for" T_{zn} at 28 weeks. During the following 5 weeks, when the urinalyses reflected a progressive deficiency of both estrogen and progesterin, toxic signs, which had previously been limited to slight albuminuria, became sufficiently alarming to render it advisable to place the patient under hospital care at 31 weeks. Two weeks later fetal death occurred.

Discussion. The finding of urinary evidence of disturbed placental metabolism starting as early as the 18th to 28th weeks in these 3 patients intimates that the primary cause or causes of the accidents of late pregnancy discussed in this paper are operative earlier than we have been led to assume from our studies of serum chorionic gonadotropin. In one of these (D.H.), values for serum C.G. were normal throughout the period of study. However, in the other 2, the first in whom urinalyses have been performed prior to any elevation of serum C.G., this elevation did not appear until at least 5 weeks after a disturbed metabolism of the estrogens was detected. The inference is that a rise in serum C.G., when it occurs, is secondary to a changed metabolism of the placental steroids. In E.S. and R.S. it was first found at 25 and 33 weeks, respectively, coincident with the first urinary evidence of estrogen and progesterin withdrawal. We are thus brought back to one of our original concepts,² that increase of gonadotropic substance may be a compensatory measure, an attempt to counteract a failing production of estrogen and progesterin. It is perhaps significant that the urinalyses on both E.S. and R.S. suggested an attempted self-correction of the steroid deficiency following the rise in serum C.G., whereas those on D.H., in whom no elevation occurred, gave evidence of uninterrupted withdrawal of estrogen and progesterin over a 6-week interval prior to intrauterine death. It is conceivable that a failure to find any increase in the level of chorionic gonadotropin reflects a deficiency in the cells secreting this hormone, whereas continued withdrawal of the placental steroids despite a rise in serum C.G., which has been the usual finding in toxemic patients, may reflect a deficiency in the placental secretion of estrogen and progesterin. Either of these situations would be readily accountable to damage of the placenta with resultant premature senility.

Since deficiency of estrogen and progesterin is the immediate precursor of the clinical mishaps discussed in this paper, administration of these hormones during the period when such accidents are likely to occur is still a logical therapeutic approach. It would appear, however, that therapy should not be limited to patients in whom an abnormal elevation of serum C.G. is detected, since such a rise does not develop in all patients with deranged metabolism of the placental steroids and is perhaps a secondary phenomenon. According to the data presented, one would expect almost as many fetal or neonatal deaths in cases whose serum C.G. was normal as in those with an abnormal elevation. A changed metabolism of the estrogens may be detected only by methods of urine analysis that are too laborious and time-consuming to be of clinical applicability. Although composite findings reveal that excretion of pregnanediol is low in patients in whom accidents of late pregnancy develop,⁴ analyses for this urinary constituent alone is of limited diagnostic significance, since normal values vary over such a wide range.^{4,10} Studies of hormones, therefore, would appear to be of little assistance in determining which patients to treat. Since the number of diabetic pregnancies seen in a year in any clinic is relatively small, and since improvements in care are sure to develop and influence

both maternal morbidity and fetal mortality, it seems to us that conclusions concerning the effect of administering hormones may be acquired only by treating alternate patients until a sufficient number of treated cases with consecutive untreated controls has been collected to be statistically significant.

The intimation that placental abnormalities are operative prior to the period of estrogen and progestin withdrawal suggests that truly preventive measures should be started even sooner, as early as the 18th to 25th weeks. Our previous studies have led to the hypothesis that products of the oxidative inactivation of estrogens in the body play an important rôle in the mechanism which controls the production of the ovarian and placental steroids. The withdrawal of progestin before normal labor¹⁰ and the regression of the corpus luteum prior to normal menstruation⁶ have thus been ascribed to a deficiency of breakdown products of estrogen accountable to a preceding period of maximal secretion of progestin and hence of reduced destruction of estrogen. The present investigation supplies our first evidence that a similar period of increased conversion and decreased destruction of the estrogens precedes the withdrawal phenomenon associated with the onset of the clinical disasters discussed in this paper. A constant supply of breakdown products of estrogen during this period of maximal conversion, such as might theoretically be provided by the daily administration of larger amounts of estrogenic material than could be metabolized in relation to the available progestin, might conceivably prolong the period of increased secretion of the placental steroids and forestall their premature withdrawal until the maternal and fetal organisms are ready for delivery.

Summary and Conclusions. Hormonal changes during pregnancy have been studied in 16 diabetic women starting between the 16th and 29th weeks. Only 8 had normal offspring, and in all but 3 some accident of late pregnancy occurred. Chorionic gonadotropin (C.G., prolan, A.P.L.) was measured in repeated specimens of serum from all 16 patients. In 8 of them, only one of whom had a normal pregnancy, the metabolism of the placental steroids was also followed by repeated urinalyses for metabolites of estrogen.

The results indicate that an abnormal rise in serum C.G. does not always precede the accidents of late pregnancy which so frequently occur in diabetic women, particularly those involving death of the offspring. Premature withdrawal of estrogen and progestin, however, such as normally develops only during the last 2 weeks of pregnancy, was a consistent finding in abnormal cases and an immediate precursor of either toxemia or death of the offspring. This change was preceded by evidence of a rate of increase in the production of the placental steroids such as normally develops only after the 36th week, this earlier abnormality being apparent at least 10 weeks prior to the clinical accident and at least 5 weeks before any rise in serum C.G. The rise in serum C.G., when it occurs, therefore, may be secondary to a more fundamental deviation from the normal, the nature of which suggests premature ripening of the placenta with ensuing premature senility.

The significance of these findings in relation to attempts at preventive therapy is discussed.

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DIABETES MELLITUS ASSOCIATED WITH ALBRIGHT'S SYNDROME (OSTEITIS FIBROSA DISSEMINATA, AREAS OF SKIN PIGMENTATION, AND ENDOCRINE DYSFUNCTION WITH PRECOCIOUS PUBERTY IN FEMALES)*

REPORT OF CASE†

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AND

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THE association of severe diabetes mellitus with the bizarre symptom complex described in 1937 by Albright and his co-workers¹ seems noteworthy, particularly since both conditions conceivably may bear some relationship to a common factor, in this instance the pituitary gland. Association of the two diseases must be extremely rare as no similar report has been recorded in the literature. Dr. Isabel Bogan,⁴ roentgenologist at the Baker Clinic, Boston, after reviewing our case with Dr. Albright, observed that although the latter has now collected more than 50 cases showing the bony changes of osteitis fibrosa disseminata, there have been no diabetics among them. The case is of further interest in that roentgenograms of the skull are suggestive of osteitis deformans, and in view of reports by Moehlig and others^{3,7,14-17} that patients having Paget's disease frequently exhibit abnormal dextrose tolerance curves of diabetic type. In the original report by Albright, the peculiar distribution of the osseous and cutaneous lesions was attributed to a neurologic or embryonic defect; while the gonadal dysfunction, which may be entirely absent in males, was regarded as

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due to a disturbance of afferent impulses to the pituitary gland. The insensitivity of our patient to insulin might lend further support to this hypothesis.

Albright's graphic description of 5 cases showing the curious triad of apparently unrelated symptoms—osteitis fibrosa disseminata, brownish pigmented areas of skin, and endocrine dysfunction with precocious puberty in females—and the subsequent report² of 2 additional cases in 1938 established this syndrome as a clinical entity. It may occur in complete or incomplete forms, depending upon whether or not one or more of the classic features is lacking. The bony dystrophy that was defined clearly by Lichtenstein¹² in 1938 and termed "polyostotic fibrous dysplasia" is apparently identical in roentgenologic, clinical, and histologic appearance, but the cases originally described did not display endocrine aspects or skin pigmentation. The latter features may be relatively infrequent in this disorder, for they are mentioned in but 4 of the 36 cases collected by Uehlinger¹⁹ and described in 1940 under the title "osteofibrosis deformans juvenilis."

The published literature was thoroughly reviewed and summarized in 1942 by Gorham, Campbell, and Rust,¹⁰ of Albany, and by Falconer, Cope, and Robb-Smith⁸ in England. Both have pointed out the great variety of titles under which earlier cases have masqueraded, *e. g.*, *pubertas præcox* und *knochenbrüchigkeit*, *osteitis fibrosa cystica generalisata*, *osteodystrophia fibrosa*, *generalized xanthomatosis of bones*, *juvenile Paget's disease*, *fibrocystic osteitis*, *fragilitas osseum*, *polyostotic fibrous dysplasia*, and even *von Recklinghausen's neurofibromatosis*. Gorham *et al.*¹⁰ tabulated 32 reported cases of the complete syndrome, and listed 19 others which did not exactly conform to the criteria enumerated by Albright as characteristic but which were considered to represent the incomplete form of the disease. Twenty of these cases had been vainly explored for adenomata of the parathyroids, 5 of them on two occasions.

In the view of Falconer *et al.*,⁸ the disease consists of a characteristic multifocal fibrous dysplasia of bone in association with endocrine disturbances which may vary in type but have skeletal precocity as the usual feature, and may include other less constant manifestations such as sexual precocity, thyroid disorders, and acromegalic changes. The case to be described is apparently the first instance in which the endocrine disorder has been diabetes mellitus; and, since the patient has been under our observation, this has been by far the predominant feature of the case.

Albright's syndrome usually appears insidiously in childhood and its active phase is terminated when adult life is reached, or when premature fusion of the epiphyses occurs. Pathologic fractures, limp, pain, or deformities are first noted. *Coxa vara* and *genu valgum* are not unusual. The quiescent phase is slowly reached, the disease is not fatal, nor does it appear to be hereditary. The diagnosis must rest on the clinical aspects, roentgenologic appearance, absence of significant alterations from normal of calcium and phosphorus levels, and if doubt still exists, on bone biopsy. Kornblum¹¹ characterizes

the typical histologic findings as thinning of the cortex of the bone, replacement of marrow and spongiosa by dense, gritty, rubbery, fibrous tissue interspersed with poorly calcified bone spicules, and an absence of cyst formation. In discussion of Kornblum's paper, Albright stated that the Roentgen examination presents 3 features which distinguish this disease from osteitis fibrosa generalisata: (1) there are areas of increased density and overgrowth of bone as well as decreased density; (2) the condition is not generalized and one should be able to find parts of the skeleton which are perfectly normal; (3) the disease practically never involves the epiphyses.

Case Report. L.T.W. (22107), age 22, a white male, was admitted to the receiving ward of the Indianapolis City Hospital on March 5, 1943, in severe diabetic coma (Rabinowitch Severity Index, 12). For a week previously he had complained of pain and swelling over the right side of the face, of excessive hunger, thirst, and polyuria, and although his mother stated that he had been a known diabetic since 1940, he had never before been in coma. Three months earlier he had discontinued his daily dose of 36 units of protamine zinc insulin and all dietary restrictions on the advice of a faith healer.

Physical Examination. The appearance of the patient was remarkable in that his face was irregularly swollen, particularly on the right side where induration involved the eyelid and pus exuded from the inner canthus. His head was asymmetrical, with prominent superorbital ridges and large malar prominences. Respiration was typically Kussmaul in type and the breath reeked of acetone. The nasal mucosa appeared congested and there was a mucopurulent blood-tinged discharge from the nares, more marked on the right side. All the teeth were loose, as if set in swollen, spongy, bleeding granulation tissue. Pus and blood exuded copiously about each tooth. Both maxillæ were tender on pressure and there was right cervical adenopathy; the heart and lungs were not apparently abnormal nor were the superficial reflexes. The brownish pigmented areas on the skin (Fig. 1) were not regarded as significant at the time but were considered "birthmarks" on the statement of the patient's mother. Exophthalmos of moderate grade was observed after recovery from coma, and a smooth palpable thyroid.

A tentative diagnosis was made of diabetic coma, acute sinusitis, cellulitis of the face, pyorrhea alveolaris, and avitaminosis. Blood was drawn for chemical determination and separate doses consisting of 60 units of unmodified insulin and 40 units of protamine zinc insulin were immediately injected. Roentgenograms of the skull were made and the patient was transferred to the ward for further treatment.

Laboratory Findings. The initial blood sugar level was 546 mg. per 100 cc. The CO₂ combining power was 12 volumes %; urea nitrogen was 60; white blood count 9100. The urine was loaded with sugar and gave 4+ acetone and diacetic acid reactions. The first roentgenogram of the skull was not very satisfactory owing to swelling of the soft tissues of the face and inability of the patient to cooperate, but there was obvious loss of translucency of all visualized sinuses, associated with mottled density of the frontal bone which suggested to the roentgenologist frontal osteomyelitis originating in the region of the frontal or ethmoid sinuses, or pathologic changes such as might be associated with Paget's disease or some other osseous dystrophy.

Course. Treatment of the coma was successfully completed within the next 12 hours, using a total of 315 units of insulin, 6000 cc. of normal saline, and 3000 cc. of 5% dextrose. The next morning a diet consisting of carbohydrate 130 gm., protein 60 gm., fat 80 gm. (providing 1480 cal.) was instituted, with separate doses of insulin and protamine zinc insulin, governed by the period urine specimens and postabsorptive and postprandial blood sugar levels. The patient's diabetes proved difficult to control, which was anticipated and attributed to infection. The temperature varied from 100° to 101° F.

for a few days, then subsided as the swelling and tenderness of the face receded, except for sporadic elevations which seemed to be related to dental manipulations attendant on treatment and extraction of some of the loosened, abscessed teeth. The diet was increased on March 16 to 150 gm. of carbohydrate, 70 gm.

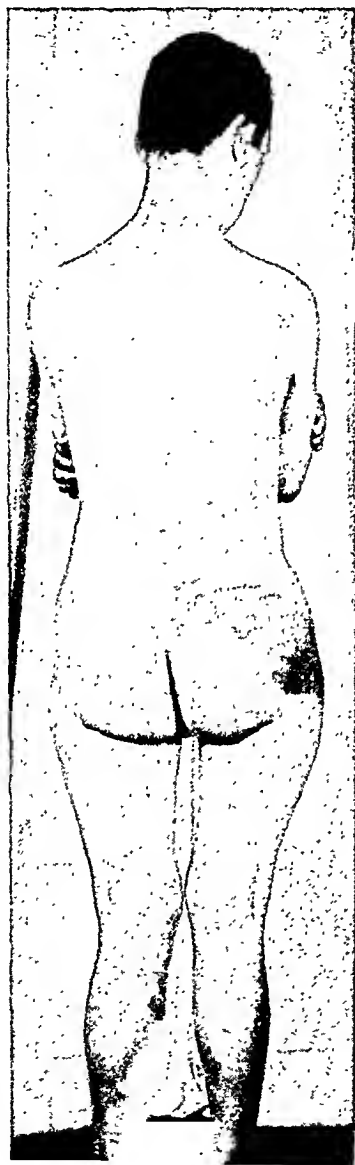


FIG. 1.—Areas of skin pigmentation. Note also the feminine configuration of the body and tendency toward genu valgum.

of protein, and 100 gm. of fat (1780 cal.), and on April 13th to carbohydrate 200 gm., protein 80 gm., and fat 120 gm. (2260 cal.), while the separate injections of insulin and protamine zinc insulin were redistributed into a single dose mixture given before breakfast in the morning. It was found that between 110

and 130 units in the ratio of approximately 3 to 1 (3 parts of unmodified insulin to 1 part of protamine zinc insulin) were required. Under this regimen, although not constantly sugar-free in all period specimens, control of fasting and postprandial blood sugar levels were reasonably satisfactory, for the patient was comfortable and demonstrated a progressive gain in weight and strength without hypoglycemic episodes. In the period from April 13th to July 1st, the average blood sugar level before breakfast was 136 mg. per 100 cc. and the afternoon postprandial levels averaged 142 mg. per 100 cc. (both taken twice each week).

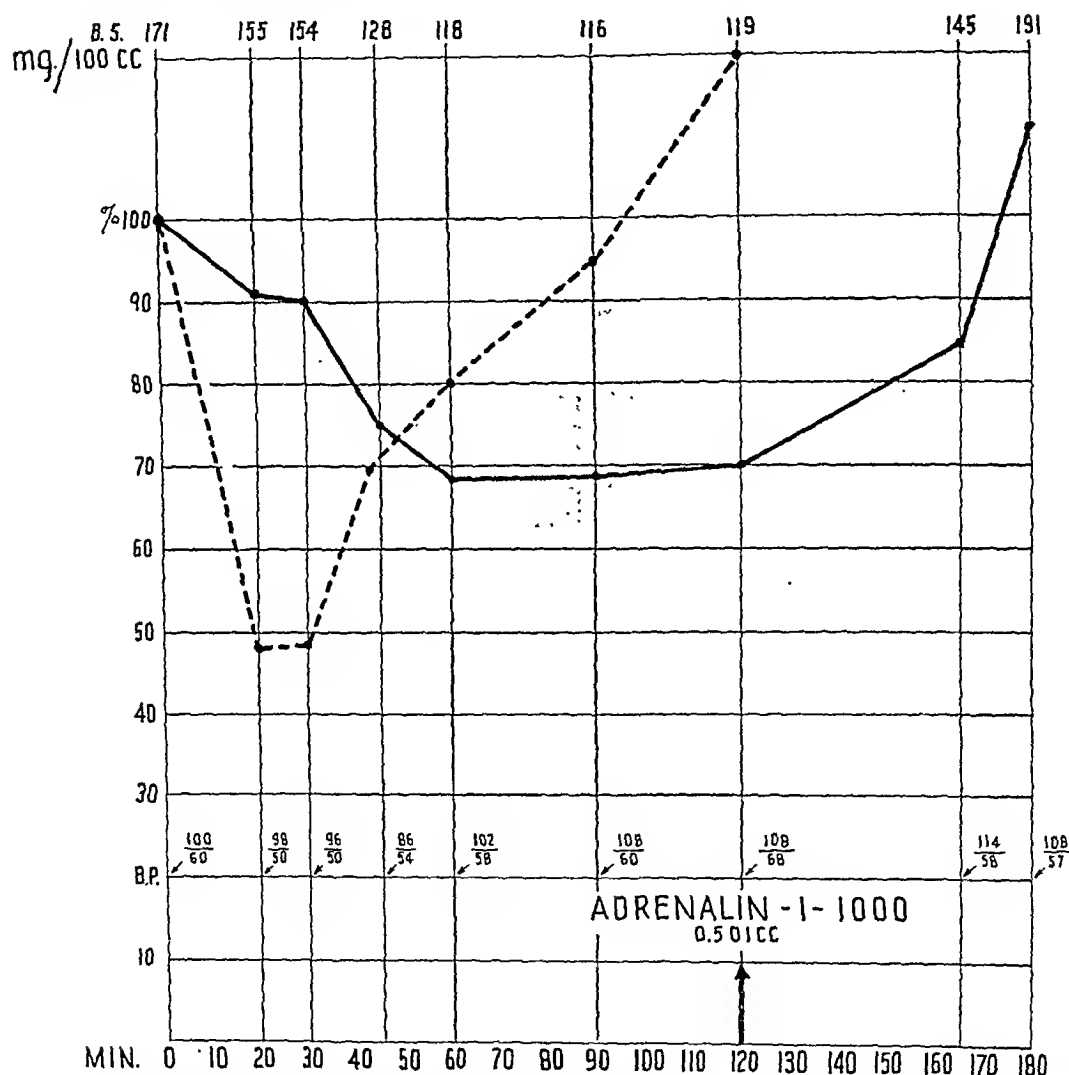


FIG. 2.—Insulin tolerance test. Broken line indicates composite normal. There is fairly marked insulin resistance followed by hypoglycemia unresponsiveness that is terminated promptly by elevation of blood sugar level after adrenalin.

Subsequent Laboratory Findings. The Kline and Kahn tests were negative; serum calcium was 9.1 mg. per 100 cc.; phosphorus 3 mg. per 100 cc.; total proteins 5.6 gm.; albumin 3.8; globulin 1.8; acid phosphatase 4.17 phenol units (King-Armstrong); alkaline phosphatase 77.2 phenol units (King-Armstrong); cholesterol 155 mg. per 100 cc. A month later the cholesterol was 150 mg. per 100 cc.; the alkaline phosphatase had fallen to 56 phenol units (1 unit = ap-

proximately 1.8 Bodansky units). Basal metabolic rates were +32% and +42% on two occasions; recheck later was +45 and +22.

In view of the high insulin requirement, an insulin tolerance test (Fig. 2) was performed on March 22, 1943 (method of Fraser, Albright and Smith⁹). The dose was 0.1 unit per kilogram of body weight intravenously (6.3 units total).

Roentgen Examinations. Roentgen rays of the upper left molars showed recurrent caries, also caries of the upper incisors with blurring and loss of detail of the bone in the region of the incisors and remaining molar. Osteomyelitis was suspected. Later Roentgen rays of the head (Fig. 5), chest,



FIG. 3.—Roentgen ray of pelvis and lower spine made in 1935 (age 15 years).

pelvis, and left leg disclosed a marked enlargement of the middle and outer tables of the skull, giving the entire calvarium a mottled appearance. The frontal sinuses and most of the maxillary sinuses were obliterated; the facial bones were less involved. There was slight distortion and enlargement of the ribs, but not approaching the degree seen in the skull. There was no increased density of the lung fields, but a reduced radiolucency of the upper two-thirds associated with the reduction in the intercostal spaces. The pelvis (Fig. 6) showed marked cystic appearing areas as well as dense, irregular striations, and marked coxa vara. The pubic bones were less involved. The femurs and the left tibia also showed the same pathologic changes but to a lesser degree.

There was evidence of old fractures of the ribs and the neck of the right femur. The scattered involvement of the skeleton as a whole is indicated in Figure 7.

Previous Admissions. Some interesting facts in the history of the patient came to light when earlier admissions under another name and number were traced. In 1932 the patient (age 12) was registered in the pediatric outpatient department, Indianapolis City Hospital, with the complaint of vomiting after eating vegetables, craving for sweets, and pain and burning in the feet. His mother stated that his appetite had always been capricious, and he

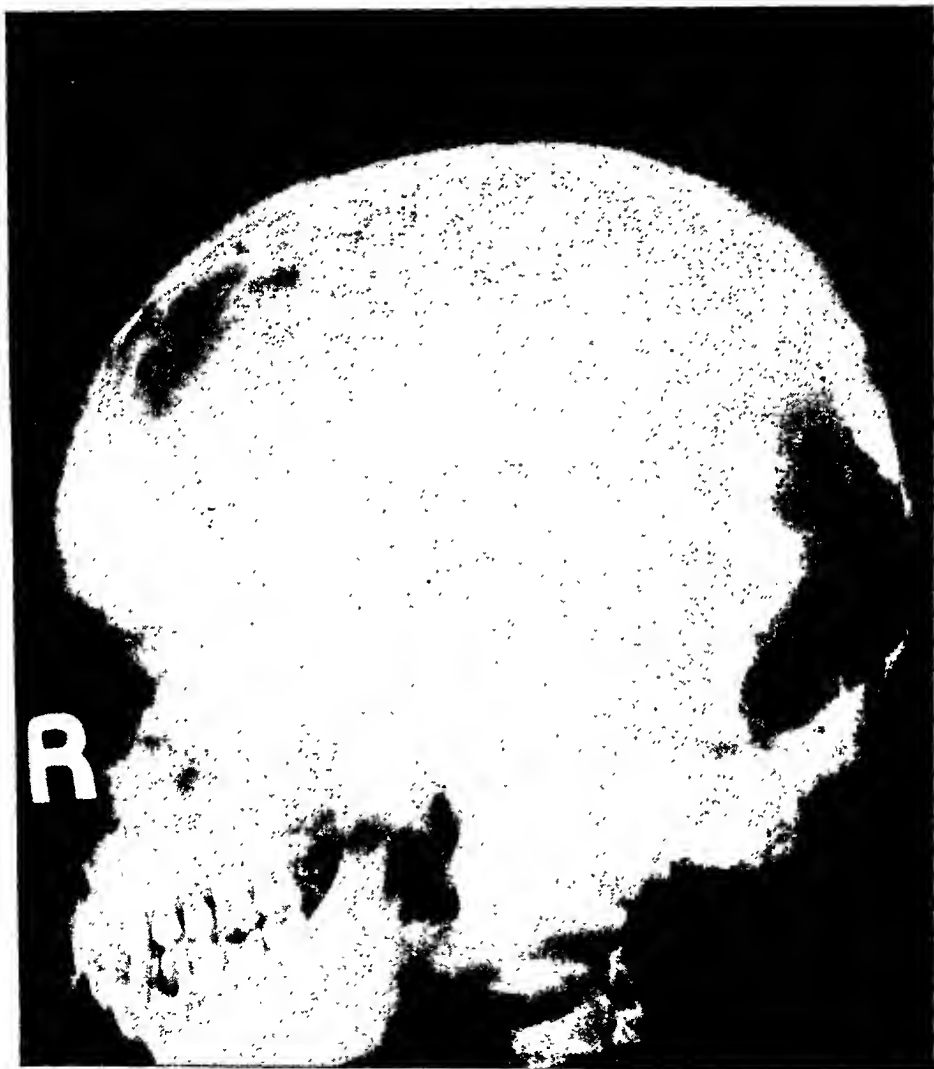


FIG. 4.—Appearance of skull in 1935 (age 15 years).

would eat no meat or dairy products but subsisted chiefly on sweet and starchy foods, and had had polyuria all his life. A note remarks the peculiar "Mongoloid facies" at the time. Viosterol and dietary corrections were prescribed. Although nocturia was present, the urine was negative for sugar. The patient was examined again on April 8, 1933 (age 13), at which time the complaint was a furuncle.

On June 27, 1935, the patient (then 15 years of age) was referred to the hospital by a private physician who had found a positive test for sugar in the

urine. The complaint was painless limping for 2 or 3 years past, a crop of boils, nocturia 4 or 5 times, sudden spells of blackness before the eyes lasting a few minutes, and nocturnal pains around the thighs and hips. It was learned that one sister had died of diabetes mellitus at age 23. Examination disclosed some atrophy of the right thigh, the right hip was 2 inches higher than the left, and Roentgen ray (Fig. 3) revealed some cystic formations in the body of each ilium and a rather granular appearance to the bodies of the vertebrae throughout the dorsal and lumbar regions, suggestive of parathyroid dysfunction. Roentgenograms of the skull (Fig. 4) showed marked density in the



FIG. 5.—Appearance of skull in 1943 (age 22 years).

base, and thickening in all flat bones. There were unusual striations in the lower half of each femur which seemed due to islands of increased calcium deposition, resembling Paget's disease. The blood Wassermann and Kline tests were negative; blood sugar determinations were 104 and 80 mg. per 100 cc. The basal metabolic rate was +3; hemoglobin 100%; red blood count 4.72; white blood count 7050; blood calcium 10.5 per 100 cc.; phosphorus 3.6 mg. per 100 cc.; total proteins 6.9 gm. per 100 cc.

In 1937, fracture of the right femur occurred which was treated at another hospital.

The next admission was in 1940 (at 20 years of age). This time diabetes was well established as the blood sugar level was 421 mg. per 100 cc. in addition to the characteristic symptoms—the complaint was of photophobia, loss of sense of smell, and peculiar feeling of tightness of the flexor muscles of the hands and calves of legs. The latter symptoms had been present about 1 year. The patient's eyes were wide set and prominent, the face was now asymmetrical owing to hyperplasia of the left malar prominence, the skull appeared larger than normal, and absence of physiologic cup in the left optic disk was noted. At this time blood calcium was 11 mg. per 100 cc. and 9.9 per 100 cc.; phosphorus 5 mg. and 3.6 mg. per 100 cc.; blood proteins 7.2 gm., 6.5 gm., and 6.7 gm.; urine sugar was 4+; red blood count 4.8; white blood count 9400; Kline and Kahn tests negative. Roentgenograms disclosed marked widening of outer and middle tables of the calvarium owing to osteolysis and osteo-



FIG. 6.—Present appearance of pelvis and upper femurs (1943, age 22 years).

sclerosis. Involvement was particularly marked in the basal bones of the skull, those of the face, and the cervical vertebrae. A cystic character in this pathologic change was more apparent in the bones of the ilium and in the femurs. Definite coxa vara of both hips and a healed fracture (1937) of the right femur were evident. Roentgen findings suggested Paget's disease or osteofibrosa cystica.

A diet of carbohydrate 200 gm., protein 60 gm., and fat 130 gm., supplying 2210 calories, was instituted, and 20 units of protamine zinc insulin each morning served to control the diabetes adequately with normal blood sugar levels. The patient then again disappeared from observation until onset of diabetic coma constituting his present illness.

Progress since the last admission has continued uneventfully. There has been a gradual increase in weight and strength, but in spite of excellent diabetic

control the insulin requirement has not declined materially (on December 9, 1943, the dose was 85 units of insulin with 30 units of protamine zinc insulin, mixed in the same syringe). The patient has returned to work, oddly enough, in a gymnasium, but is careful to protect himself from possible injury.

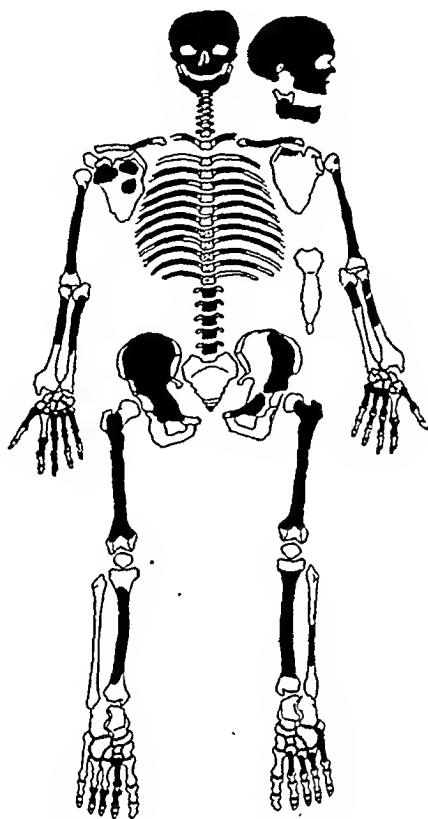


FIG. 7.—Main areas of skeletal involvement (1943).

Comment. The cause of this curious disease is unknown. Obviously it would be unwise to base any etiologic conclusions on this one case, which may or may not be merely a rare coincidence, since diabetes develops in one of 200 to 250 persons in the population and there is a history of diabetes in the patient's family. Nevertheless, it should serve to direct attention to what appears to be a common finding if it is looked for; namely, depressed glucose tolerance in certain of the osseous dysplasias such as Paget's disease. The appearance of severe diabetes and finally coma in our case, together with enlargement of the mandible as demonstrated by Roentgen ray, is suggestive clinically of acromegalia; while the exophthalmos, elevated basal metabolic rate, and goiter also point toward the pituitary as a factor. The insulin tolerance curve seems to support this possibility, and in addition the lack of responsiveness to hypoglycemia suggests adrenal involvement.

Recently Sternberg and Joseph¹⁸ published the pathologic findings in the case reported several years previously by McCune and Bruch¹⁸

when the patient was 4 years old. Exophthalmic goiter was a prominent feature in this case, and it is pointed out that its occurrence as a part of the syndrome is significant enough to be other than coincidental. On autopsy the important endocrine changes were hyperplasia of the thyroid, thymus, and lymphoid structures, mature cystic ovaries, a narrow "lean" adrenal cortex, normal parathyroids, and the pituitary showed basophilic hyperplasia with adenoma formation. The picture was that of a gland showing evidence of prolonged stimulation and activity, especially of the basophil cells. When this case was originally reported there was slightly depressed glucose tolerance and glycosuria after 1.75 gm. of glucose per kilogram of body weight. No neurologic lesion was found. Cushing,⁶ in describing the clinical manifestations of basophil adenomas, observed that exophthalmus, osteoporosis, and sometimes glycosuria were not infrequently associated with certain types of pituitary adenomata and that the diabetes in such instances was far more difficult to control than is that of pancreatic origin. No pituitary tumor was found in Coleman's⁵ case, the only other autopsy reported thus far.

It is generally agreed that precocious puberty in females having the disease cannot be directly attributed to pituitary tumors. However, this type of precocious puberty is observed following hypothalamic lesions. Albright originally proposed that the characteristic triad of symptoms might result from an embryologic defect in the region of the hypothalamus. The facts that the areas of pigmentation have been present since birth of our patient, and that the osseous lesions were well developed at the time he first came under observation, seem significant in this connection.

Summary. 1. The first known case of diabetes associated with Albright's syndrome has been presented. Osteitis fibrosa disseminata, areas of skin pigmentation, and further endocrine dysfunction taking the form of mild exophthalmic goiter were observed.

2. Insulin resistance and unresponsiveness to hypoglycemia were demonstrated by the insulin tolerance test and are regarded as suggestive of a complex endocrine disturbance, possibly originating before birth, and implicating the pituitary gland.

NOTE: Since submission of this report another case, the 34th to be described in the literature, has been published (Dockerty, M. B., Meyerding, H. W., and Wallace, G. T., *Proc. Staff Meet. Mayo Clin.*, 19, 81, 1944). Although this patient showed precocious somatic development and menstruated at 7 years of age, she reached middle age before the disease was discovered, after a pathologic fracture. The status of the carbohydrate metabolism was not described.

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A NOTE ON IRRADIATION SICKNESS*

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NAUSEA, vomiting, headache, cramps and diarrhea which often complicate the course of therapeutic irradiation comprise the syndrome of Roentgen ray sickness reviewed lately by several investigators.^{2,3,6,7} Our interest in the problem dates from the successful use of nicotinic acid in treating patients with these complications;⁴ and the discovery that the behavior of urinary pigments and the codehydrogenases I and II following irradiation of the upper abdomen over the spleen resembled that in severely ill pellagrins.¹ As much evidence had accumulated to suggest other analogies between Roentgen sickness and certain dietary deficiency states, it was planned to make a comprehensive investigation of the effect of a standard dose of irradiation upon normal well-fed subjects; upon those given a vitamin B-deficient diet⁵ with and without supplements of some of the vitamins in which the diet was deficient; and upon pellagrins and upon persons whose poor diet had caused ill-health without other stigmata of a specific deficiency syndrome. Studies on normal persons have not been reported previously. We are continuing this study but the results so far seem of sufficient importance to warrant publication at this time.

* The very heavy expenses of this study involving the special services of so many experts was made possible by the Research Corporation, the Nutrition Foundation, and Standard Brands, Inc.

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Material and Studies. Of 16 subjects chosen for study, 5 were nutritionally normal persons hospitalized for some injury from which they were convalescing at the time of the experiment (2 white females, 1 white male, 2 colored males). One normal white male was treated after 6 weeks of control on the vitamin B-poor diet,⁵ and again after a course of nicotinic acid. Three pellagrins (1 white female, 1 white male, 1 colored female), 3 persons with mild pellagra (1 white female, 2 white males), a white female with mild peripheral neuritis and 3 white females with subclinical vitamin B deficiency were irradiated under various conditions of vitamin therapy and dietary control.

The radiation was given in all instances after an overnight fast (13 to 16 hours after eating). An area over the spleen and upper abdomen was used. Four hundred Roentgen units were administered from a distance of 20 cm., using a Thorous filter, 200 K.V., 20 ma. at the rate of 33 R. units per minute.

Tests for the codehydrogenase, biotin, riboflavin, pantothenic acid and nicotinic acid content of the blood were made before, and 6 and 24 hours after treatment in most cases. In some instances pyruvate and glutathione were determined. The urinary pigments were studied in daily 24 hour specimens before, and in 6 and 18 hour specimens after Roentgen ray.*

SYMPTOMS AFTER 400 R-UNITS TO UPPER ABDOMEN

		ANOREXIA	NAUSEA	VOMITING	HEADACHES	ABD. CRAMPS	DIARRHEA	PROSTRATION	SHOCK
W.F.- 40	(Subclinical deficiency) - control diet- 2wks.	+	+	0	+	+	+	0	0
W.M.- 33	(Mild pellagra)- control diet- 3wks.	+	+	+	+	+	+	±	0
	after 50 mg Thiamin for 4 days	+	±	0	0	0	0	0	0
W.M.- 45	(Mild pellagra)- control diet- 15 days	+	+	+	+	+	±	+	0
	after 300 mg. Nic. Ac. for 4 days	+	0	0	0	0	0	0	0
W.F.- 36	(Mild neuritis)- control diet- 12 days	+	+	+	+	+	+	+	+
W.M.- 46	(Pellagrin) Treated with 400mg Nic. Ac., 50mg Thiamin + 3 mg riboflavin daily for 1 mo.	0	0	0	0	0	0	0	0
C.F.- 40	(Pellagrin) control diet- 14 wks	0	0	0	0	0	0	0	0
	500mg. Nic. Ac.- 6 wks.	+	+	0	0	0	0	0	0
	without Nic. Ac.- 6 days	+	+	0	0	0	0	0	0
C.M.- 42	(Normal)	0	0	0	0	0	0	0	0
C.M.- 39	(Normal)	0	0	0	0	0	0	0	0

FIG. 1.—Comparison of symptoms following Roentgen therapy in normal persons and those with mild or severe pellagra. In 3 of the deficient subjects the effects of irradiation with and without a preliminary period of therapy with thiamine or nicotinic acid are compared.

Results. Following irradiation of the type described above, the normal persons consuming a good diet or on various vitamin B supple-

* We are particularly indebted for the laboratory tests to Dr. and Mrs. Ansel Swain, Dr. R. E. Eakin, Dr. S. P. Vilter, Dr. Gwei Djen Lu and Mrs. Sue S. Sanders. Miss Monette Springer, R.N., and Mrs. Jane M. Mann, R.N. contributed most efficiently in applying methods to insure rigid restriction as to diet. The tests and normal diets were devised by Miss Jean M. Grant, Nutritionist, who also supervised the dietary controls. Prior to beginning this experiment she made a detailed dietary assessment of each patient and his family.

ments had no ill-effects, except nausea in 1 white woman. The syndrome of irradiation sickness in varying degrees of severity occurred in the rest of the patients, including the normal person who had subsisted on the vitamin B-deficient diet⁵ for 6 weeks. The symptoms in several subjects are recorded in graphic form in Figures 1 and 2.

	8-5	19	20	21	22	23	24	25	26	27	28	29
Anorexia	o											
Nausea	o	±	+	+	+	o	o	o	±	o	o	o
Vomiting	o	o	+	+	o			o	o			
Headache	o	o	+	o				+	±	o		
Cramp	o	o	+	+	o			o	o			
Diarrhea	o	o	+	+	o			o	o			
PYRUVATE		0.61	0.20	0.96				0.71	0.41	0.42		
BES	o	±	+	+	+	+	+	+	+	+	o	+
BES + Nitrites	o	+	+	+	+	+	+	+	+	+	+	+
X RAY		X							X			
Thiamin					50	50	50	50	50			
DIET	control	→	→	→	→	→	→	→	→	→	→	→

PELLAGRIN in REMISSION White Female 40

FIG. 2.—The effect of thiamine on reaction to irradiation. The control diet, one poor in B-complex vitamins, is the same as that used in previous experiments.⁶

	5-3	7-8	8-18	19	20	21	22	23	24	25	26	27
Anorexia	+	o	o	o					o	+	+	+
Nausea	+	o	o	o					o	+	+	o
Vomiting	+	o	o	o					o	+	o	
Diarrhea	+	o	o	o					o	o		
BES	+	o	o	o					o	o	o	o
BES + Nitrites	+	o	o	o					o	+	+	+
X RAY			X						X			
NICOTINIC ACID		500 mg daily										
DIET	control	→	→	→	→	→	→	→	→	→	→	→

PELLAGRIN COL. FEMALE 40

FIG. 3.—The effect of nicotinic acid on reaction to irradiation in a pellagrin on the vitamin B-poor diet.

Figure 2 shows also the result of pyruvate studies, and compares the results of irradiation before and after a supplement of thiamine. In Figure 3 the procedure was reversed. Roentgen therapy had no unpleasant effects after nicotinic acid had been given during the last 6 weeks of a period of more than 3 months on the control diet, but a

week after the nicotinic acid supplement was discontinued the same amount of irradiation produced the characteristic reaction of Roentgen sickness. In all the cases studied there was a rough, but by no means exact, correlation between the severity of the reaction and the degree of vitamin depletion as gauged clinically. The most extreme reaction occurred in the woman with mild peripheral neuritis, who actually went into shock, with cold, sweating, cyanotic skin, impalpable pulse and systolic blood pressure of 80 mm. Hg. The man whose previous food habits were satisfactory had a mild and brief, though definite, reaction after 6 weeks on the vitamin B-deficient diet.

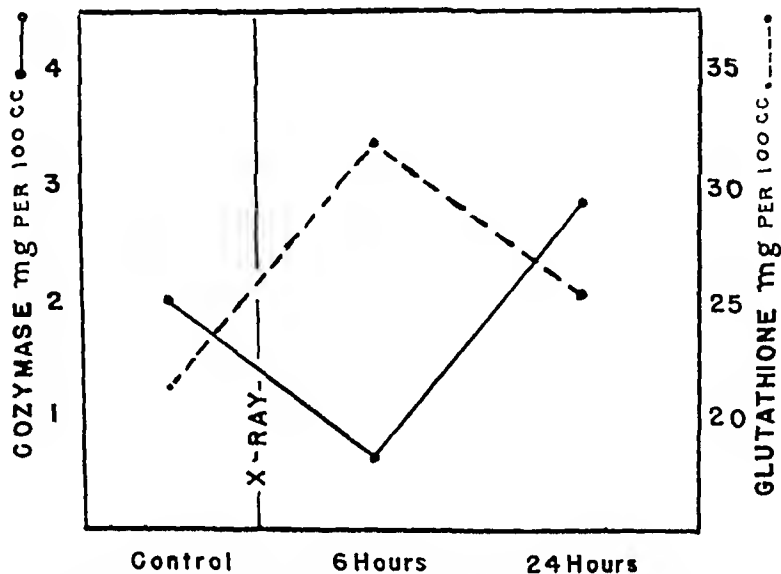


FIG. 4.—Changes in concentration of cozymase and glutathione in the blood of 2 subjects with pellagra following irradiation.

In some instances attempts were made to allay the symptoms by injection of large doses of thiamine or nicotinic acid, or both, but once the reaction was established these substances were of relatively little value, though it was our impression that they did help to a moderate extent. Other studies made in Cincinnati in which similar doses of the same vitamins were injected shortly before radiotherapy showed them to be relatively ineffective. When, however, a series of Roentgen ray treatments was given, and the irradiation syndrome occurred after the first treatment daily oral or intravenous vitamin B supplements were followed by a decrease in the distressing symptoms. Since the psychic factor is difficult to evaluate, control injections of physiologic solution of sodium chloride were tried, and not always without apparent help, so this phase of the problem needs more careful study on a much larger series of cases before conclusions are drawn. In the Birmingham study all subjects received tablets of some kind, so that they were not aware of the type of supplement and could not discriminate between placebo and vitamin except when the nicotinic acid produced flushing. A repetition of the experiment using the amide of



FIG. 5.—A, Classical example of Casal's necklaee or cravat. Note also the forlorn mask-like facies. B, Symmetrical pellagrous dermatitis of the elbows, forearms and wrists over pressure areas.



A



B

FIG. 6. A. Dermatitis of the forearm and hand characterized by thickening and p

nicotinic acid has not been carried out but should be in order to eliminate the psychic element in the experiment.

Chemical Studies. There was no significant change in the blood level of biotin, pantothenic acid, riboflavin or nicotinic acid. Figure 4 shows the reciprocal relation of glutathione and cozymase levels. The fall in the coenzymes had been observed previously,¹ but the increase of glutathione or some similar reducing substance had not been noted before. Its significance remains obscure. The pigments in the urine appeared in excessive amounts, as had been found in a previous study.¹

The above observations, under controlled conditions, suggested to the authors that we should include this representative case report of a patient who developed deficiency states following repeated Roentgen ray therapy:

Case Report. L. V., 41 year old negro woman, was brought to the Nutrition Clinic of Hillman Hospital in June, 1943, with a "breaking out" on the skin of 2 months duration.

F.H. and P.H. irrelevant.

P.I.: She was in good health until June, 1942, when she noticed for the first time abdominal pain and a bloody foul vaginal discharge. In August, 1942, she came to the Hillman Hospital and a diagnosis of carcinoma of the cervix, Grade 2, and of a large myomata uterii was made. Roentgen therapy was started and from then until April, 1943, 40 treatments were applied to the lower portions of the abdomen. Following each treatment she became severely ill. She developed nausea, vomiting and profuse sweating, and on 4 instances apparently went into "shock." This "x-ray sickness" caused her to vomit all food and water for 2 or 3 days and then for another day or two she had little or no desire for food. Accordingly, she ate little and retained rather little of that scant amount. Still later in the treatment (she does not remember just when) her desire for any food of any kind disappeared and by this time she did not go a full day without nausea and vomiting. Finally she took no solid food but frequently "drank strong coffee to give myself strength." About the first of May, 1943, she noticed large areas of deep pigmentation over the arms, feet, hands, legs and neck. The same day she noticed blurring of vision, excessive lacrimation and photophobia. Two weeks later she noticed severe pain and weakness and paresthesias of the legs and excruciating burning of the feet and ankles. At some indefinite time preceding this she noticed "trembles," "crawling sensations" of the flesh, became "fractious," screamed when she heard noises, and could not bear to see anyone. All these symptoms became even more pronounced during the first 2 weeks of May. She states that by this time she had become so sensitive that when anyone talked to her she cried and that her memory was so poor she could not go from one room to another in her own house without feeling lost. She said, "Doetor, you can never know how weak and dizzy and foolish-headed I am." In June, she developed burning and soreness of the mouth, tongue, throat, and salivation had increased to the point where she actually drooled large amounts. At this time she was having from 10 to 12 loose bowel movements daily.

She reported regularly to the tumor clinic until early in May when she became so weak a friend took her to her home. She left no forwarding address and efforts to locate her failed. Finally the friend became so alarmed about her condition she brought her to the tumor clinic. From there she was referred to the Nutrition Clinic and admitted immediately to the hospital for treatment.

Physical examination showed a well-developed, emaciated negro woman (the body weight had decreased from 247 to 129 pounds within a year). Large and small well-demarcated areas of crusted, deeply pigmented, inelastic skins covered the elbows, forearms, hands, knees, ankles, feet and scapulae and

extended around the neck to form a collar of Casal (Figs. 5, 6). The tongue was edematous with transverse fissures, atrophic at the tip and edges with an occasional greatly hypertrophic red papilla. Neurologic examination showed greatly diminished muscle power and tone but no selective weakness. There was great increase in calf and peripheral nerve tenderness. Position sense was good. Vibratory sense was decreased approximately 30% in the upper extremities and 50% in the lower. Pin prick and light touch were normal.

Clinical impression: Characteristic pellagrous dermatitis, glossitis, stomatitis and nutritional peripheral neuritis (beriberi). The prognosis is considered that of carcinoma and myomata uterii.

Discussion of Case. Carcinoma and deficiency diseases are both notorious causes of loss of body weight but none of the visiting physicians or Dr. Walter B. Frommeyer who studied this patient in great detail could see that the tumor process in the cervix could obstruct alimentation sufficiently to produce nutritional deficiency symptoms of the degree of severity seen in this case. Her diet had been satisfactory, and she had never had nausea, vomiting or loss of weight until after the Roentgen ray treatments. We learned years ago that when, for any reason, a great deal of vomiting or diarrhea occurred severe deficiencies are likely to develop very quickly. It appears that the tissues of the body gradually adjusted but there came a time in May (the usual season for the symptoms of pellagra to appear) when the body tissues could no longer adjust and lesions in every way typical of pellagra appeared. The fulminating type of pellagra seen in this case developed within a year whereas without the predisposing factors—nausea and vomiting—years of ill-health and frequent recurrences precede an attack of this type.

Summary. The effect of administering a measured quantity of irradiation to the left side of the upper abdomen has been studied.

Persons on a diet poor in the vitamin B complex developed Roentgen sickness, which could be prevented or reduced in severity, by giving supplements of nicotinic acid or thiamine for a few days before irradiation.

Well-fed persons had little reaction to the same dose of Roentgen rays which made the vitamin B-deficient persons sick.

The practical application of these results toward the prevention or reduction in severity of irradiation sickness by means of nicotinic acid and thiamine is suggested by these findings. A patient with carcinoma and myomata of the uterus is reported in considerable detail since she was given repeated Roentgen therapy which in each instance was followed by severe irradiation sickness. She was not given supplements of nicotinic acid or thiamine and subsequently developed classical pellagra and beriberi.

Conclusions. Though unqualified conclusions are not justified from the few cases it has been possible for us to study adequately, it would appear that the optimum time for vitamin therapy is before and not after the syndrome of irradiation sickness appears and that such therapy is essentially preventive in nature. If, as we have suggested,¹ the basic disorder in Roentgen sickness is a disturbance in respiratory enzyme systems, this approach to the problem deserves careful clinical

application. The fact that nutrition is often deranged in persons needing radiotherapy makes the use of careful dietary and vitamin therapy logical, if on empiric grounds alone.

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A NEW PRACTICAL METHOD FOR SUBCUTANEOUS ADMINISTRATION OF HEPARIN

PRELIMINARY REPORT

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IN 1916, while working in Howell's Laboratory, MacLean¹³ accidentally discovered a substance which proved to be highly anticoagulant. Howell recognized the significance of this substance, and in 1918 named it "heparin"⁹ because of its abundance in the liver. The application of heparin to the treatment and prophylaxis of thrombo-embolic disease remained dormant, however, until Charles and Scott² succeeded in preparing a purified barium salt of heparin which afforded a practical source of supply. Schmitz and Fischer,²³ who worked independently in Copenhagen, also had succeeded in obtaining a pure brucine salt of heparin. As a result, extensive experimental and clinical trials of this pure heparin were carried out by various investigators, particularly Best and Murray^{1,17-22} in Toronto, and Jorpes, Holmgren and Wilander¹⁰ in Sweden.

The work of these investigators and of others^{7,8,15,16,24} established the value of heparin in vascular surgery and in the therapy of phlebotrombosis and thrombophlebitis. The beneficial action of heparin in the therapy and prophylaxis of postoperative pulmonary embolism has also been stressed.³⁻⁵ In view of its ability to inhibit, in adequate dosage, the formation of blood platelet thrombi, heparin has had extensive appeal in subacute bacterial endocarditis.^{6,11,14} At the present time, the clinical application of anticoagulant therapy in war surgery is of paramount importance.

A review of the literature indicates that anticoagulant therapy has been effective in a wide variety of conditions. Unfortunately, the

more widespread use of heparin, admittedly the safest and most rational of the anticoagulants, has been retarded by the necessity for its administration by continuous venoclysis or by periodic intravenous injections as suggested by Crafoord and Jorpes.³ Of these two methods of administration continuous venoclysis is preferable due to the ephemeral effect of the individual doses in the fractional method. However, continuous heparinization by venoclysis for protracted periods of more than 2 weeks is virtually impossible of accomplishment. Moreover, the expense entailed has been an important deterring factor because of the huge amounts of heparin required to reach therapeutic levels.

In reporting on a new method of administering heparin originally devised for animals,¹² it was stated that the method was being adapted for humans. This method of depositing heparin subcutaneously in animals was arrived at after numerous attempts with pellet and glass capsule implantation. This latter approach had to be abandoned because of erratic, unpredictable results, the necessity for instrumental procedure and the obvious impracticability of sustaining heparin effects over prolonged periods.

To accomplish a slower and more equable absorption of heparin, the Pitkin menstruum* was adopted as a vehicle. This menstruum was developed to regulate the rate of release of water-soluble drugs injected intramuscularly or subcutaneously. The ingredients are: gelatin, 15 to 30%; dextrose, 5 to 12%; acetic acid, 1 to 1.5%; distilled water, *q. s.*, to 100%. The viscosity of the menstruum, which is predicated on the concentration of the gelatin and dextrose, determines the rate of liberation of the drug; the greater the viscosity, the slower the liberation. In the preparations containing heparin the optimum percentages of gelatin and dextrose were 18% and 8%, respectively.

The menstruum is made so that it liquefies at 80° F. Below this temperature it remains in a solid state. Its preparation is a rather delicate procedure as some of the ingredients oxidize readily and deteriorate with heat. It is best to prepare the menstruum by first dissolving the gelatin in distilled water, with a moderate degree of heat and double the desired percentage strength. After the gelatin has been thoroughly dissolved in the distilled water, it is placed in a sterile container to which a negative pressure (vacuum) is attached in order to draw out the air bubbles before it is allowed to solidify. Twice a day for 2 days it is liquefied with moderate heat, never over 110° F., and subjected to the negative pressure while in the liquid state. On the 3rd day it is liquefied, and the dextrose and acetic acid, in excess, are added. The mixture is then placed in a vacuum boiler and boiled for 15 minutes. When partially cooled (110° F.), sterile distilled water is added in sufficient amount to bring the percentage strength of the gelatin, dextrose and acetic acid up to the desired level. At

* We wish to acknowledge with thanks the kindness and coöperation of the late Dr. George P. Pitkin in furnishing us with details for the preparation of the Pitkin menstruum.

this time the eueupin dihydrochloride is added for its anesthetic and antiseptic properties. The solution is again placed under negative pressure and allowed to solidify. It is liquefied daily for 5 days and bacteriologic tests made. If free of contamination at the end of 5 days, the heparin, epinephrine hydrochloride, ephedrine sulfate and chlorbutanol are then added. The preparation, while in a liquid state, is distributed in 1 to 2 cc. sterile ampules which are immediately sealed in the usual fashion with heat. The ampules are again subjected to the routine bacteriologic tests. From the moment the gelatin is dissolved, all utensils, containers, ampules and so forth must be sterile and the solution handled thereafter with aseptic precautions. After the eueupin, heparin, epinephrine, ephedrine and chlorbutanol have been added, the temperature should never be raised above 110° F. The preparation when ready for use is of a light amber color.

Ampules containing varying proportions of heparin* and Pitkin menstruum with or without vasoconstrictor elements, were prepared. All ingredients apart from heparin were found to be inactive in control tests.

The contents of the ampules were liquefied at 110° F., drawn up through a 2½-inch, 19-gauge needle into a previously warmed, sterile 5-cc. or 10-cc. syringe and immediately injected subcutaneously, preferably in the anterior or lateral aspect of the thigh. Intragluteal injections were also done in a limited number of instances. Although this method of administration was abandoned because of too rapid absorption, further experience may eventually prove it to be just as effective as by the subcutaneous route. When 2 ampules were employed, the contents were thoroughly admixed in the syringe before injecting. The material congealed promptly following inoculation. The injections were administered with a minimal amount of discomfort to the patient. Some patients subsequently complained of pain, tenderness, and swelling at the site of inoculation, particularly when a large amount (3 to 4 cc.) of the menstruum was used. This, however, did not prove to be a deterrent to further treatment, and symptoms promptly subsided upon cessation of therapy.

The initial formula (LP) contained 100 mg. of heparin (Table 1). During extensive trials† with this formula, it was found that at times there was a preliminary lag of several hours before any appreciable rise in coagulation time developed. This was then sustained to varying degrees for periods of from 2 to 5 days (Chart 1). In most instances there was a prompt rise and in some a sharp drop to the control levels. In these latter cases the crystals of heparin could be seen floating freely within the menstruum and were not strictly incorporated in the vehicle. The rapid absorption of these crystals resulted in a short-lived heparin effect. In other cases, following a preliminary sharp rise and fall in coagulation time, there was a second

* We are indebted to the Roche-Organon Company for their generous supplies of heparin.

† We wish to thank Dr. J. Rosenthal of the Jewish Hospital and Dr. A. M. Rabiner of the Jewish Sanitarium and Hospital for Chronic Diseases for permitting us to utilize their service cases for this phase of our work.

dary rise and more gradual fall to the base line. In these cases it was assumed that the heparin was partially in solution, the primary rise being due to prompt absorption of the free crystals; the secondary effect was ascribed to the more even and slower absorption of the menstruum with its dissolved depleted heparin. Experiments were also carried out in which heparin was administered intravenously at the same time or shortly after the LP formula was given subcutaneously. In these "primed" cases, there was a rapid rise in the coagulation time and precipitous fall which was then followed by a more sustained effect as the LP material was absorbed.

TABLE 1.—HEPARIN-PITKIN FORMULÆ

	LP (mg.)	LP-8 (mg.)	LP-9 (mg.)	LP-10 (mg.)	LP-11 (mg.)
Cryst. sodium salt of heparin	100.0	200.0	100.0	100.0	200.0
Epinephrine hydrochloride	1.0	1.0	1.0		
Ephedrine sulfate	25.0	25.0	25.0		
Chlorbutanol	0.5	0.5	0.5	0.5	0.5
Eucupin dihydrochloride	1.0	1.0	1.0	1.0	1.0
Pitkin menstruum <i>q. s. ad</i> . . .	1.0 cc.	2.0 cc.	2.0 cc.	2.0 cc.	2.0 cc.

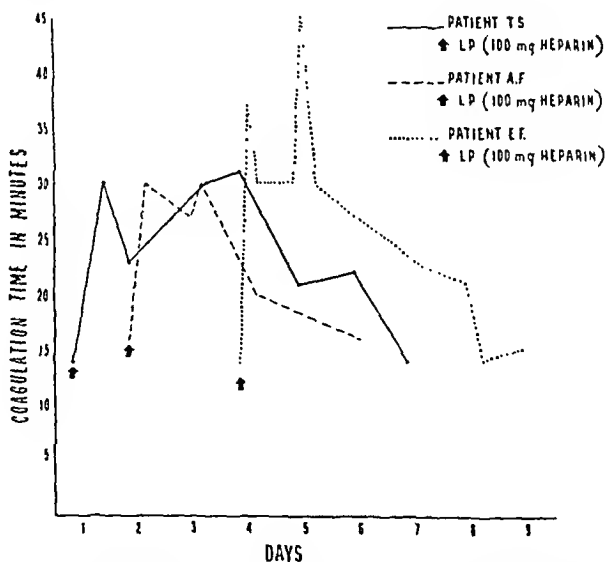


CHART 1.—Patient T. S. Injected with LP (100 mg. heparin). Note sustained augmentation of coagulation time for 5 days. ——— Patient A. F. Injected with LP (100 mg. heparin). Elevation of coagulation time for 3 days. Patient E. F. Injected with L.P. (100 mg. heparin). Note 4-day heparin effect.

In order to overcome these shortcomings, the formulæ were revised (LP-8, 9, 10, 11; Table 1). The amount of Pitkin menstruum was increased to 2 cc. in order to accommodate the greater dose of heparin. LP-10 and LP-11 (Table 1) were devised so that the dose of heparin could be stepped up without adding to the vasoconstrictor elements.

The effects of formulæ LP-8, 9, 10 and 11 were evaluated singly and in combination in the course of 242 experiments performed on 51 patients. Some of these served merely as controls. Many patients suffering from thrombophlebitis, phlebothrombosis or subacute bac-

terial endocarditis have been and are still being satisfactorily heparinized by this method.

It was possible by combining the various formulæ to initiate heparinization with liberal doses of the drug and then to maintain adequate heparinization with smaller doses or by spacing the injections. This has been done in actual practice, so that satisfactory results have been attained over protracted periods (5 weeks) with but 2300 mg. of

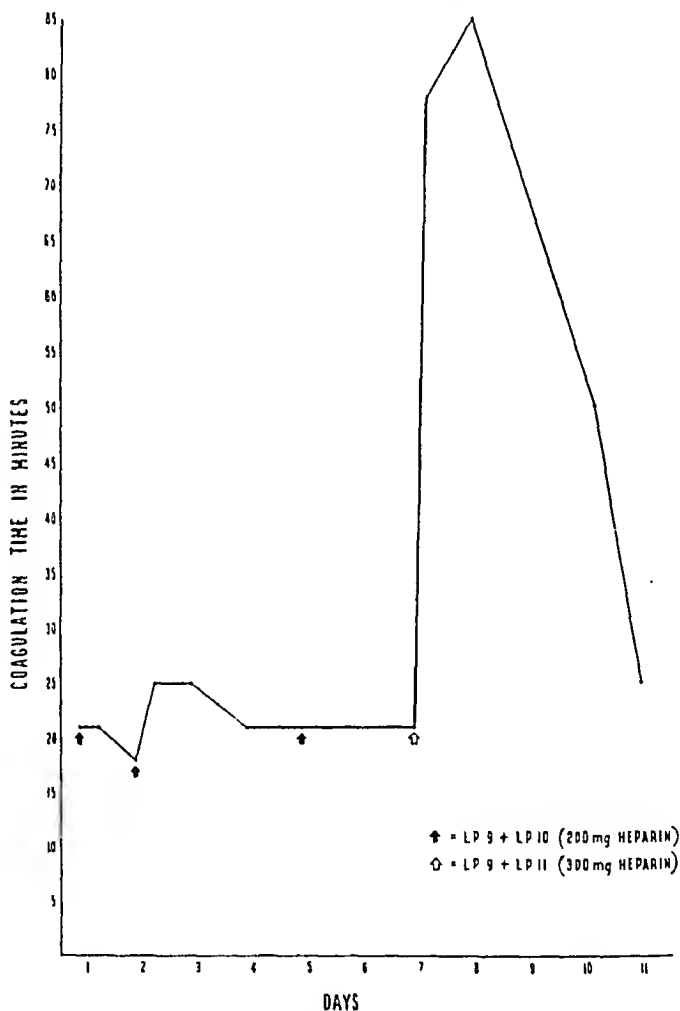


CHART 2.—*Patient T. G.* The repeated injection of 200 mg. heparin resulted in little or no augmentation of the coagulation time. The injection of 300 mg. heparin, however, yielded a prolonged effect which extended over 3 days.

heparin (Case 1). This contrasts with a comparable requirement of at least 10,500 mg. of commercial heparin were it at all possible to administer it by the cumbersome technique of continuous venoclysis.

Although no precise quantitative investigations were carried out, the impression was gained that heparin requirements paralleled body weight. This is illustrated in Chart 2. This patient, a tall individual weighing 190 lbs., responded little or none to the repeated injection of

200 mg. of heparin (LP-9 and 10). The injection of 300 mg. (LP-9 and 11), however, resulted in a rapid and sustained effect.

Representative cases demonstrating therapeutic applications of this method of heparinization over prolonged periods are the following:

Case Studies. CASE 1. *Thrombophlebitis of veins of pelvis and lower extremities* (Chart 3). D. S., a white female, aged 24, was admitted to the Jewish Hospital, service of Dr. E. L. Shlevin, on 1/9/43, complaining of fatigue, low-grade temperature, anorexia and loss of weight. She was delivered of a stillborn, 9½ month fetus on Oct. 30, 1942. Her postpartum course was



FIG. 1.—Venograms of lower extremities of Case 1. A, Right lower extremity. There is an accessory saphenous vein present. Beading in the column of opaque medium (see arrow) is noted. This is indicative of the presence of multiple thrombi. None of the opaque medium enters the popliteal, posterior tibial, or femoral veins. These findings indicate an extensive thrombotic process involving these vessels. B, Left thigh. The popliteal vein is outlined to a point about 5 inches above the knee joint (see arrow). Beyond this point dye cannot be demonstrated although a considerable amount has passed into the upper portions of the saphenous vein. These findings indicate obstruction in the deep femoral vein in its upper two-thirds.

uneventful until November 15, when she developed swelling of the right leg, pain and fever. She was treated with bed rest, but the symptoms persisted. The swelling of the leg progressed and the temperature did not recede. She was then given sulfathiazole and sulfadiazine. The temperature regressed slightly with chemotherapy, but edema of the lower extremity spread to the thigh and groin. On December 12 the patient was allowed out of bed. The next day the temperature rose to 103° F. Sulfadiazine was again given and continued to the time of admission. She complained also of nausea, vomiting,

backache and slight dry cough. *Physical examination:* On admission the patient appeared well developed and well nourished. The temperature was 102° F., pulse 100 and blood pressure 120/80. Both extremities were swollen and edematous and there was pelvic tenderness. *Clinical impression:* A diagnosis of thrombophlebitis involving the veins of the lower extremities and pelvis was made. Venograms were done on 1/15/43 (Fig. 1). These showed obstruction of the deep left femoral vein in its upper two-thirds. Right venography revealed multiple thrombi in the saphenous vein adjacent to the lower portion of the femur and extensive thrombotic involvement of the femoral, popliteal and tibial veins. Chemotherapy was discontinued, and heparin therapy was instituted on 1/16/43 by administering subcutaneously 2 cc. each of LP-9 and LP-10 containing a total of 200 mg. heparin. From a control level of 14 minutes, the coagulation time rose to 55 minutes within 24 hours. It was maintained continuously between 45 and over 75 minutes; averaging about 55 minutes. Injections of 200 mg. of heparin were given on

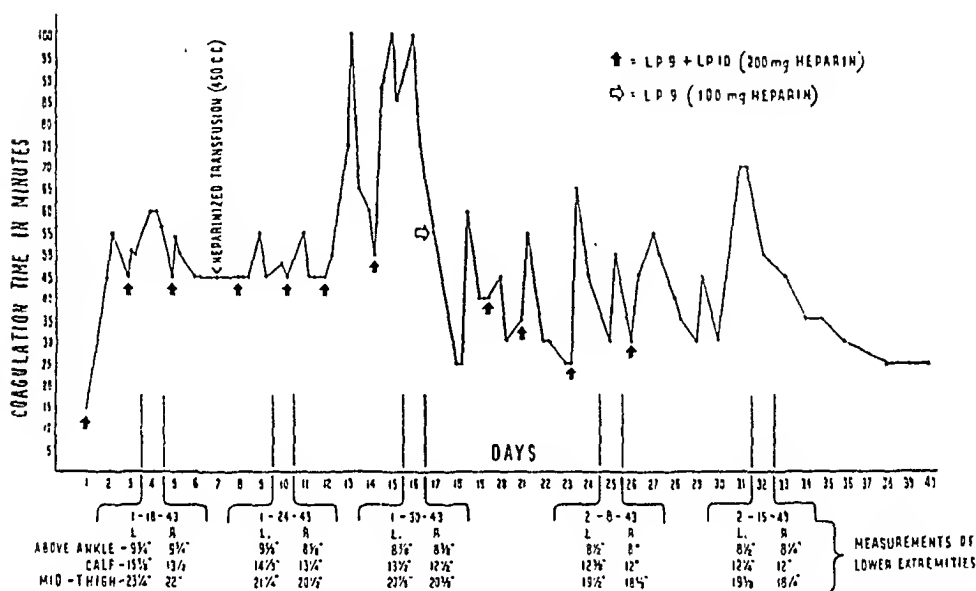


CHART 3.—Patient D. S. Thrombophlebitis of pelvic and femoral veins treated with heparin administered by the subcutaneous route. Therapy was continued successfully for 5 weeks. A total of only 2300 mg. of heparin was required.

an average of every 2nd or 3rd day. *Clinical course:* The temperature dropped dramatically following cessation of chemotherapy, and remained within normal limits except for an occasional rise to 100° F. The measurements of the lower extremities were as recorded on Chart 3. The clinical response to heparin therapy was highly satisfactory. There were no additional therapeutic measures except for a transfusion of 450 cc. of heparinized blood on 1/21/43 to combat moderate secondary anemia. There was a slight febrile reaction to the transfusion. Of interest was the successful heparinization over a period of 5 weeks requiring a total of but 2300 mg. of heparin.

CASE 2.—*Phlebotrombosis, postoperative.* M. G., a white male, aged 44, was admitted to the Jewish Hospital, service of Dr. Leo M. Davidoff, on 10/24/42, for laminectomy to remove a herniated intervertebral disk. The postoperative course was uneventful until 10/30/42 when the patient complained of pain in both lower extremities. On 11/18/42 severe pain and tenderness were present in the left thigh and leg. *Physical examination:* The circumference of the left thigh and leg was considerably greater than the right. Edema was also noted, which became more evident the next day.

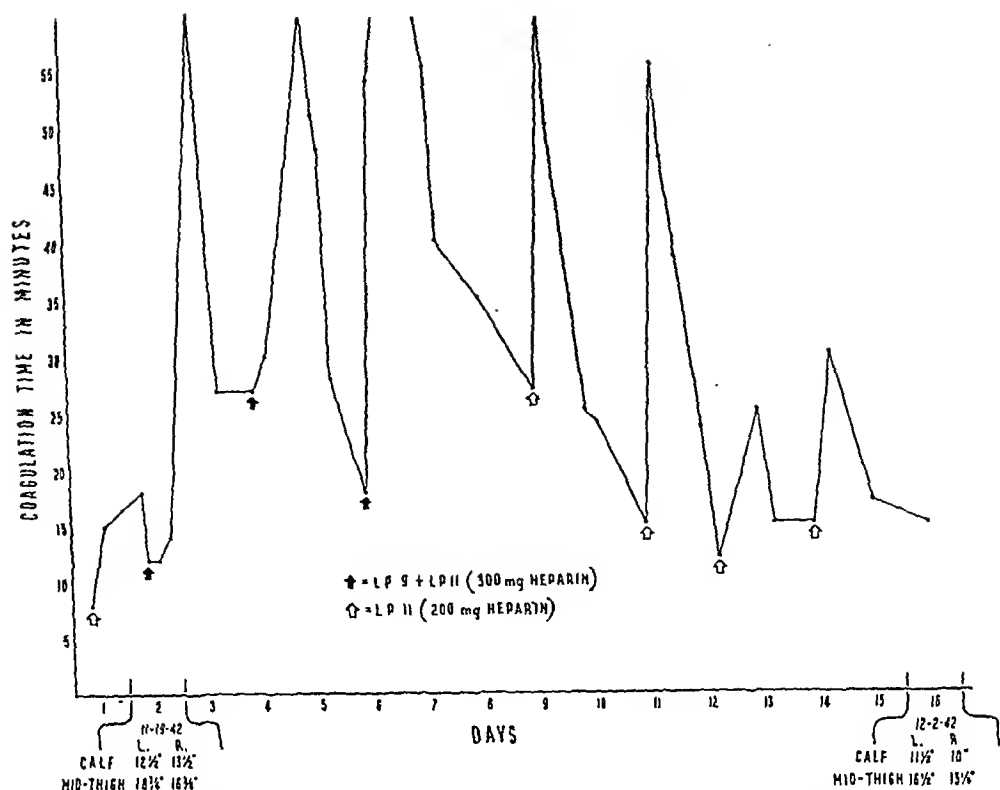


CHART 4.—Patient M. G. Postoperative phlebothrombosis treated with heparin administered by the subcutaneous route. Treatment was carried out for 16 days. A total of only 1900 mg. heparin was used contrasted with the usual requirement of from 4000 to 4800 mg. heparin by the intravenous method.

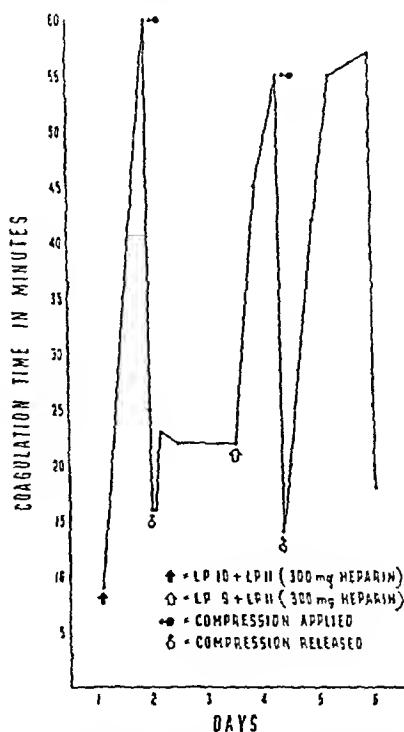


CHART 5. Patient H. T. Effect of compression on heparin effect. Note precipitous drop in coagulation time with suspension of heparin absorption due to application of compression. Following release of compression, heparin is again liberated with resultant prompt rise in coagulation time.

Comparable measurements of both extremities may be noted on Chart 4, which also portrays graphically the progress of heparinization. *Clinical impression:* A diagnosis of phlebothrombosis of the deep venous channels of the left lower extremity appeared justified. Heparin therapy was advised and instituted on 11/19/42. *Clinical course:* A total of 1900 mg. of heparin was used over a period of 16 days. Coincidental with the heparin therapy there was a cessation of the phlebothrombotic process. After 1 week of heparinization, a marked improvement was noted in the leg with respect to the swelling and tenderness. This clinical improvement continued, and it was reflected by recession of the edema as indicated by the measurements (Chart 4). The patient was discharged from the hospital without residua.

Discussion. The therapeutic response portrayed by the foregoing cases has also been observed consistently in a number of other patients. These observations will be incorporated in a comprehensive clinical report. The present communication is devoted primarily to the description of a new method for producing a satisfactory heparin state that is safe, easily achieved, practical and economical.

As compared with our normal of 12 to 20 minutes for humans,* a coagulation time of from 30 minutes to 2 hours was considered an adequate heparin response. In practically every instance an acceptable prolongation of coagulation time was observed and the effects of a single deposit were apparent for 24 to 72 hours or more. On no occasion did any complications arise nor were any toxic symptoms noted. Despite the gratifying results obtained thus far with the formulæ at hand, additional experience may disclose the need for further revising the proportions of the various ingredients.

With the method of heparinization by continuous venoclysis, its mere discontinuance will result in a return of the coagulation time to normal within a few hours. For a more abrupt termination of the heparin state, the intravenous injection of whole blood or protamine has been advocated.

With the technique of subcutaneous administration of heparin as here described, no instantaneous withdrawal of the heparin effect is as yet feasible. However, whole blood or protamine may be employed to neutralize the free heparin, while compression about the site of inoculation will effectively suspend its further liberation. This was demonstrated in a case of subacute bacterial endocarditis successfully heparinized by our method. Injections were made as usual in the lateral or anterior aspect of the thigh. Compression was effected for 1 to 3 hours by means of a tourniquet above or a compression cup about the site of injection. Chart 5 depicts the precipitous drop in coagulation time which followed the compression and the prompt rebound which ensued with the release of compression.

Prolonged heparin therapy by the usual means of continuous venoclysis is economically prohibitive to a large group of patients regardless of its proven merit. The use of this subcutaneous method of heparinization, while not yet commercially available, gives promise of sharply

* The coagulation times in all instances were determined by the Lee-White modification of Howell's method. (GRADWOHL, R. B. H.: *Clinical Laboratory Methods*, St. Louis, C. V. Mosby Company, p. 514, 1943.)

curtailing the cost of this anticoagulant agent because of the reduced heparin requirement and ease of administration.

Summary. A simple, safe, and practical method for the subcutaneous administration of heparin has been devised. Its clinical application has been successfully attempted in 15 cases of thrombophlebitis and phlebothrombosis.

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MENINGOCOCCUS INFECTIONS WITH ARTICULAR COMPLICATIONS

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In these days, with meningococcic meningitis assuming importance as an epidemiologic problem, attention must be focused on one feature of the disease which is not sufficiently emphasized. Articular involvement of meningococcic etiology is not uncommon, and frequently presents important diagnostic and therapeutic problems. Although this complication has been by no means neglected in the literature, and an analysis of the subject by Herrick and Parkhurst⁹ in 1919 represents an orderly approach to this confusing manifestation of the disease, nevertheless few publications are available since the introduc-

tion of the sulfonamides. This is not, as might be suspected, because of the fact that the problem no longer occurs. Chemotherapy seems to have effected little, if at all, the incidence of joint involvement during the disease. Since meningococcic meningitis is again assuming importance in World War II, literature on this aspect of the disease is well in order.

Review of the Literature. The first clinical mention of the condition was given by Welch²³ as far back as 1810. In a report to the Massachusetts Medical Society, he spoke of "swellings . . . in some cases (of cerebrospinal fever) . . . in the joints and limbs . . . and their appearance has been compared to that of gout." This was over three-quarters of a century before the discovery of the meningococcus itself by Weichselbaum. North¹⁴ mentioned "swelling like rheumatism of the joints." Still²² and Gwyn⁸ not only reported some cases, but demonstrated the organism for the first time in the joint fluid, blood and cerebrospinal fluid. The condition did not escape the keen, clinical eye of Osler^{15,16} who reviewed the literature up to the beginning of the present century, and presented cases of his own experience. The French literature¹⁹ contains many detailed descriptions. World War I afforded an excellent opportunity for study of the disease, and accordingly the most scientific accounts of the joint manifestations have resulted. Rolleston,¹⁷ in England, and especially Herrick and Parkhurst⁹ in the United States, have undoubtedly made the most valuable contributions to the subject. In the peace years between the last war and the present, little has been said outside of the reports of isolated cases by Jaffe,¹⁰ Kobayashi,¹² and Campbell and Greenfield.² A few articles on the doubtful entity of postmeningitic spondylitis have also appeared. One exception on the relative silence on the subject was the article by Schein,²⁰ reporting on 23 cases of his own experience. Recently Cattell³ gave the first report of meningococcal arthritis in a patient who had been treated with the sulfonamides. Their case, not dissimilar to the one presented here, was also found to yield purulent joint fluid on aspiration. They point out that "meningococcic arthritis with purulent effusion is a rarity." How much of a rarity it actually is, as well as other questions on the entire subject, will probably be answered by the medical workers in our Armed Forces.

Clinical Classification. We are indebted to Herrick and Parkhurst⁹ for a practical classification of types of arthritis, but it must be realized that their classes are not always sharply demarcated, and also that several types may occur in the same patient, as in the case presented here. They spoke of 3 types.

Type A. In this group falls the "rheumatic" type of joint involvement, *i. e.*, the multiple-joint arthralgias occurring during the first few days of the disease as part of the general picture of the meningococcemia. It occurs simultaneously with the other features of meningococcic sepsis, notably the purpura. Pathologically, there is a purpura of the joints, so to speak, if Herrick is right in describing peri- and intra-articular hemorrhage as the cause (*cf.* section on pathology). Clinically the pain, redness, and tenderness are marked, though swell-

ling is at a minimum. It is a symmetrical polyarthritis, affecting any of the joints. Its duration is short and frequently merely transitory, often being overshadowed by the usually dramatic picture of the primary disease, or overlooked in an irrational or comatose patient because of its subjective rather than objective character. Herrick was probably correct in considering these cases as particularly severe ones, but his grave prognosis for meningitis cases with Type A articular involvement no longer holds, for the severe bacteremia of these cases offers no special barrier to the marvelous sulfonamides. The joint manifestations may actually precede the meningeal (by as much as 2 months, according to Schein), and the patient then presents a picture of rheumatic or gonorrheal arthritis. The difficulties of diagnosis in such an instance are obvious; indeed, our Jamaican patient had joint symptoms a full day before these of the central nervous system, and it would have been impossible to have forecasted his meningitis at that time.

Type B. While the ankle involvement in our patient definitely belongs in Type A, his knee joint lesions are an excellent example of this B group. Here the arthropathy has its onset later in the disease, usually after the 5th day. It is usually monoarticular (if more than one joint is involved, one takes precedence over the others), and the knee is the joint most frequently involved. Effusion is the predominating feature of this type. Pain, redness, tenderness, and limitation of motion are reported by most observers to be *characteristically* at a minimum; but we find ourselves in complete agreement with Schein²⁰ and Cattell³ that the effusion is by no means silent in all cases. Herrick and Parkhurst⁹ felt that this arthropathy occurred in mild cases of meningitis, and they considered the general prognosis of the patient to be good. We have not found this complication to be dependent on the severity or mildness of the disease; and the reason for their favorable outlook was probably because of the fact that if the patient had survived up to the appearance of the complication, his natural powers of resistance would probably carry him through the rest of the disease. Meningococci are reported to be found in the joint fluid in one-third of the cases. The fluid itself may be mucinous, serous, seropurulent, or frankly purulent. Pathologically it appears to be an infectious lesion, in contrast to the hemorrhagic character of Type A joints (*cf.* section on pathology). Its duration is relatively long, and occasionally it is not without lasting effects on the joints themselves.

Type C. Herein fall the cases of arthralgias and arthropathies occurring as part of the well-known serum sickness. Its importance is small now that serum therapy of meningitis has become outmoded. It is related in no way to meningococcic meningitis and may occur in any disease where serum is given. It is an aseptic, serous type of arthritis, an urticaria of the joints, so to speak. Signs and symptoms are moderate, duration is short, and the prognosis is excellent. Coca⁴ found the incidence of joint pain in serum sickness to be 1 to 2%. Schick,²¹ quoted by Schein,²⁰ stated that "articular pains seldom occur but can be intense and annoying, involving large or small joints, often

only one joint, the conditions being marked by transience and absence of objective symptoms." As Schein points out, this type (which occurs after the 6th day following the serum injection by any route) has its onset at the same time as Type B. As there are no absolutely differentiating characteristics, it is difficult to be certain with which type one is dealing but, we must reiterate, this problem will no longer be of any concern.

TABLE I.—ARTICULAR INVOLVEMENT IN MENINGOCOCCUS INFECTION

Patient	Sex	Age	Joint involved	Onset (day of disease)	Treatment (of primary disease)	Treatment of complication	Duration	Result
H. M.	M	7	Lt. elbow	7th	Serum—intra-muscular, venous, thecal	Aspiration (10 cc. purulent material)	2 wks.	Asymptomatic
W. O'C.	M	19	Rt. knee Lt. knee	5th 6th	"	Conservative	Over 2 wks.	Sl. amt. of pain and stiffness in both knees on discharge from hosp.
E. S.	F	36	Lt. shoulder	7th	"	"	3 days	Asymptomatic
D. C.	M	20	Lt. knee	7th	"	"	2 days	"
C. C.	M	34 mos.	Both ankles Lt. knee Lt. ankle	1st 8th 15th	Sulfathiazole	" Aspiration Conservative	2 days 2 wks. 2 days	" " "
E. H.	M	39	Lt. knee	11th	"	"	10 days	"
J. P.	F	15	Both ankles	1st	Sulfadiazine	"	2 days	"
L. S.	M	20	Rt. knee	6th	"	"	2 wks.	Asymptomatic—but still slightly swollen
R. B.	M	3	Rt. wrist Rt. knee	15th 16th	"	"	5 days 1 day	Asymptomatic "
L. H.	M	48	Rt. elbow	1st	Sulfathiazole	"	3 days	"

Postmeningitic Spondylitis. This doubtful entity was described by Epstein,⁶ and later by Billington.¹ In view of its rarity and its occurrence always at the lower lumbar spine, it is possible that it is in reality a postpuncture affair, a cellulitis, a spinal osteomyelitis, or even, as Schein²⁰ suggests, herniation of the nucleus pulposus due to injury to the protecting annulus fibrosis by the spinal needle.

Sulfatoxic Arthritis. This entity, though rare, may make its appearance during the disease in view of our newer methods of treatment. Its rarity is attested to by the fact that authoritative reviewers of sulfonamide toxicities either fail to mention such an occurrence, or merely speak of transient arthralgias. Long *et al.*,¹³ however, say: "Painful joints have been reported in the course of sulfanilamide therapy and we have noted several patients who have received sulfathiazole had exquisitely tender, swollen joints." They emphasize that this occurrence may confuse the treatment of gonorrhea because of its resemblance to gonorrheal arthritis. Glicklich and Sherman⁷ report a very interesting case in which the arthritis was in all probability of chemical origin. This was a case of chancroidal infection, treated with sulfathiazole, in which the knees and elbows became tender and swollen with effusion. They aspirated 50 cc. of clear, sterile (on culture), serous fluid containing a few polymorphs per high-power field and 4.1 mg. per 100 cc. of sulfathiazole. Coincident with this were other manifestations of drug toxicity. The Ducrey lesions had disappeared by this time and the drug was stopped; the joint symptoms then sub-

sided. One week later, after a test dose of 3 gm. of sulfathiazole, the full picture of drug toxicity (including the joints) returned. The drug was stopped immediately, and the patient became asymptomatic in 12 hours. A high protein level (above 3.2%) of the joint fluid and a sugar content markedly lower than that of the blood definitely suggests an infectious rather than a toxic arthritis, but until more data is had on "sulfarthritis" this cannot be regarded as an infallible differentiating test.

We have spoken of Type A arthritis as purpuric, Type B as infectious, and Type C as urticarial. It is perhaps wrong to call the condition an arthritis. It is, rather, a synovitis, or at the most a peri-arthritis, but actual involvement of the osseo-cartilaginous tissues may occur. Keefer *et al.*¹¹ give the most recent and perhaps most accurate knowledge of joint lesions. "Meningococcic arthritis is a metastatic lesion involving first the deeper synovial tissues" (Type A of Herrick). "Later," (Type B) "infection invades the superficial cells with effusion of fluid into the joint cavity and varying degrees of destruction of the cartilage. It is essentially a metastatic acute synovitis." This, Cattell³ implies, makes Herrick's⁹ classification meaningless, since his Types A and B are but varying degrees of severity of the same "ens morbi." Even if this be true, and Herrick's grouping be worthless from a pathologic standpoint, it is still a most useful clinical classification. Certainly, much more study of the lesions postmortem must be done.

Incidence. Rolleston¹⁷ of England reported an incidence of 4.8% of articular involvement in meningitis. Councilman *et al.*⁵ reported 5.4%, Herrick's series showed 6.5%. A series at the Bellevue Hospital revealed an incidence of 7.7%.²⁰ Sainton¹⁹ believes this complication to be much more common, occurring in some degree in one-fifth of the cases. At our South View Hospital 10 cases of arthritis have occurred among 266 cases of meningococcus infection within the past 12 years.

Four cases of articular manifestations occurred among 215 patients during the 10-year period previous to the advent of chemotherapy. Six cases occurred in the past 2 years among 51 cases of meningococcus infections treated only with sulfa drugs. The wide difference between 1.9% incidence before, and 11.8% occurrence since the use of chemotherapy may well be accounted for by the lessened mortality with more opportunity for complications during convalescence due to the life-saving benefits of the sulfonamides.

Case Study. The case of meningococcic meningitis presented here is of special interest, first in that it included two types of arthritis, and second because of the rare type of purulent articular involvement occurred after the meningeal infection had been cured by an adequate blood level of sulfathiazole. The patient was a 22 year old Jamaican who had been in this country only a few months. He was doing agricultural work at Winneconne, Wis., as part of the Government's effort to solve the manpower shortage problem. He became ill while at work and was taken to the Milwaukee County General Hospital with severe pain in both ankles as his chief complaint. Headache, sore throat, stiff neck, and fever were his other entrance complaints. Interestingly, 5 months before, while still in his native land, he developed ankle pain during

the course of yaws. At this time he received arsenicals, and the joint pain disappeared. His main request now of the examining physician was for "another injection" to relieve his ankle pain.

Physical examination revealed a well-developed, well-nourished colored male who tossed about in bed during the examination and complained constantly of his head and ankles. His left pupil was large and round and did not react to light. The right was small and round and reacted. Ears and nose were normal. The pharynx was moderately injected, tonsils were small, and the teeth were in good repair. His head was held absolutely rigid, and attempts at flexion elicited an inconclusive Brudzinski sign. There was no cervical adenopathy. Examination of the chest revealed unrestricted respiratory excursions, normal lung resonance, normal breath sounds, and absence of râles. The heart size was normal, the rate moderately rapid and the rhythm regular. The abdomen was soft and non-tender; there were no palpable organs or other masses. Inspection of the ankles failed to reveal any evidence of pathologic change, but there was extreme pain on palpation and on active and passive motion. Patellar reflexes were absent bilaterally. Kernig's sign and the Babinski reflex were also absent. The temperature on entrance was 102.2° F. rectally, pulse 88, and respiration 20. Total white count was 16,600. On lumbar puncture, cloudy fluid under 25 mm. Hg pressure was obtained. This contained 18,075 leukocytes per c.mm. with a predominance of polymorphonuclear leukocytes. There were a few large gram-negative diplococci extra- and intra-cellularly, which proved to be meningococci on culture. Sugar was absent, protein 250 mg. per 100 cc., and chlorides 700 mg. per 100 cc. The patient was given 6 gm. orally of sulfadiazine in the first 8 hours and was then transferred to the South View Isolation Hospital.

Here he was placed on large doses of sulfathiazole orally. On repetition of lumbar puncture, cloudy fluid was obtained under slightly increased pressure, containing 8370 leukocytes per c.mm. (71% polymorphs, 29% lymphocytes). Smear showed numerous pus cells, few lymphocytes, and occasional gram-negative diplococci resembling meningococci (although culture was negative). Dextrose was 33 mg. per 100 cc., and protein 64 mg. per 100 cc. Blood and cerebrospinal fluid Kahn tests were negative. The urine was negative except for a trace of albumin, which, however, was absent on subsequent urinalyses. Six days after entrance, the total white blood count was 10,200 and 5 days later was 8520 with 64% polymorphs (53% segmented and 11% non-segmented), 28% lymphocytes, 7% monocytes, and 1% eosinophils.

On the 6th day of the disease, after having received 29 gm. of sulfathiazole, he developed marked pain in his left knee. This rapidly became warm and swollen, and on the following day 40 cc. of greenish purulent fluid were aspirated. The fluid contained numerous pus cells, but no organisms could be demonstrated on smear. In all, 350 cc. were aspirated on 5 occasions, and the fluid finally became serous in character and contained only a few pus cells. On the 12th day of the disease he developed a painful moderate effusion into the left ankle joint and at the same time a skin eruption, consisting of numerous small papules over the trunk and extremities. The drug was continued and the rash disappeared in 2 days, the ankle swelling subsiding, without aspiration, in 4 days. The blood level of sulfathiazole at this time was 11 mg. per 100 cc. and blood culture was negative. The joint fluid had a level of 310 mg. per 100 cc. of the total drug, and culture of the fluid was negative. On the 18th day of his disease, the patient was transferred back to the Milwaukee County General Hospital for convalescent care, completely asymptomatic, but with apparently a small amount of fluid in the left knee joint. Roentgenograms showed no significant change in either knee joint.

Discussion. Little has been said about the actual direct etiologic agent. The most likely explanation is a metastatic invasion of the synovial membranes by the meningococcus itself, these tissues acting as "loci minoris resistentiæ" during the septicemic stage. Herrick's observation of the presence of the bacteria in one-third of the joints

would seem to bear this out. However, one must wonder at the failure of the "sulfa" drugs to lower the incidence of the complication. Perhaps the infection becomes quickly localized and therefore resistant to the drug. Perhaps the joint lesion is a hypersensitivity response. Or maybe a symbiotic virus infection is the cause of the joint lesions. The possibility of one or more of the 12 strains of meningococcus being viciously arthrotropic must be thought of. Indeed, one is forced to speculate on the amazing similarity between the gonococcus and the meningococcus. The latter differs from the former in the ability to ferment maltose and in being less uniform in size. Otherwise the resemblance is startling. And, as a matter of fact, their tissues of predilection may be the same; the gonococcus can invade the meninges as well as the joints and the same is true for the meningococcus. Indeed, a case of urethritis resembling gonorrhea in every respect showed meningococci on bacterial examination. Sabah and Faham¹⁸ reported a case of gonorrheal arthritis successfully treated with polyvalent antimeningococcus serum.

Summary. 1. The literature dealing with articular complications of meningococcus infections has been reviewed to date.

2. The incidence of articular involvement during the course of epidemic meningitis for patients at the South View Hospital has been compared with experience elsewhere.

3. In our series of 215 patients treated with sulfa drugs the incidence of arthritis was 1.9%, in comparison with an incidence of 11.8% arthritis among 51 patients receiving sulfonamides.

4. A case record of a monarticular purulent synovitis has been presented.

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PRIMARY AND SYMPTOMATIC AMYOTROPHIC LATERAL
SCLEROSIS

A CLINICAL STUDY OF 81 CASES*

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THE contradictory results we obtained in our experimental investigation of the effects of vitamin E and other vitamins in the treatment of amyotrophic lateral sclerosis naturally raised the question whether the disease was one entity due to a constant etiologic factor or a clinical syndrome of varying etiology. To answer this question we studied intensively 81 patients personally observed between 1939 and 1942. Of this group we would designate 68 as primary; the rest, although also fairly typical clinically, we would regard as symptomatic. The two are discussed separately.

We did not include atypical or so-called transition cases, and rigidly excluded cases of progressive spinal muscular atrophy and lateral sclerosis, because we regard them as different entities. Most writers, it seems to us, are not definite on this point. The recent paper by Swank and Putnam⁵ dealt with amyotrophic lateral sclerosis and "related conditions." In 1935 Petersen³ reported on 22 cases. Dana's¹ older study of 70 cases obviously included a large number of progressive muscular atrophies.

Amyotrophic lateral sclerosis has always been regarded as a system disease involving the old and new motor systems, and it is known to follow a fairly consistent clinical course. As we studied the incidence of "types," the various modes of onset, unusual manifestations, possible etiologic or precipitating factors, and clinical variants, we began to doubt the unitary concept. All our patients were observed over long periods of time, up to 3 years, many to a fatal termination and necropsy, and we were able to study the life history of the disease. Without anticipating conclusions, we may indicate that our study justifies the tentative opinion that amyotrophic lateral sclerosis appears to be not one single disease entity but a syndrome of variable etiology, and that there are at least 3 different types which manifest themselves more or less the same clinically.

General Etiologic Factors. *Sex.* Table 1, giving the number of men and women according to age groups, shows a male-female ratio of

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2:1 in the primary group. The usual ratio is given as 3 or 4 to 1.⁹ In the bulbar types, the sex incidence is said to be reversed, but this was not true of our 22 cases.

Age. Though practically all age groups were represented, the greatest number occurred between 30 and 69 (Table 1). The youngest case in our series was a girl 16 years of age and the oldest a man of 74.

TABLE 1.—DISTRIBUTION OF CASES ACCORDING TO SEX AND AGE AT TIME OF ONSET

Age	Men	Women	Totals
10-19	0	1 (16 yrs.)	1
20-29	2 (20, 23 yrs.)	0	2
30-39	10	5	15
40-49	12	7	19
50-59	15	6	21
60-69	7	2	9
70-79	1 (74 yrs.)	0	1
Totals	47 (70%)	21 (30%)	68

Nationality, Occupation and Heredity. Fourteen national groups were included in the series, but there were no Orientals and Negroes. All varieties of occupation were represented, without anyone predominating. There was no history of familial incidence of amyotrophic lateral sclerosis in any of the cases, so that hereditary factors can be excluded.

Other Etiologic Factors. Table 2 summarizes other possible etiologic factors which may be discussed in some detail.

TABLE 2.—POSSIBLE ETIOLOGIC AND PRECIPITATING FACTORS

	Cases
I. <i>Dietary and gastro-intestinal:</i>	
(a) Inadequate diet	3
(b) Marked weight loss, preceding onset	6
(c) History of gall bladder disease with restriction of fatty foods	3
(d) Restriction of diet because of "dysentery"	1
(e) Recurrent ulcer with gastro-enterostomy	1
(f) Unsuspected gastro-intestinal pathology discovered at postmortem	3
II. <i>Inflammatory:</i>	
(a) Severe upper respiratory infection at onset	2
(b) Syphilis	1
(c) Previous acute poliomyelitis	1
III. <i>Vascular:</i>	
(a) Diabetes	1
(b) Arteriosclerosis with thrombo-angiitis obliterans and coronary artery disease	1
(c) Marked generalized arteriosclerosis, clinically	5
IV. <i>Toxic:</i>	
(a) Exposure to gasoline	1
(b) Exposure to lead (painters)	2
(c) Exposure to heavy metals (electroplater)	1
(d) Spinal anesthesia	2

Dietary and Gastro-intestinal. Of 68 cases, 16 gave a history of dietary deficiency or gastro-intestinal dysfunction. The diets of 3 were definitely inadequate (Cases 7, 8, 32). Six patients (Cases 20, 44, 47, 48, 53, 67) gave a history of marked weight loss. Three patients (Cases 25, 38 and 41) had a history of gall bladder disease with restric-

tion of fatty foods from 1 to several years. One (Case 9) gave a history of restricted diet for 3 years because of diarrhea due to "dysentery." Another (Case 17), had a gastro-enterostomy for ulcer with recurrence 1 year before the onset of amyotrophic lateral sclerosis. Finally, in 3 of the 11 cases that came to necropsy, the unsuspected findings were carcinoma of the pancreas, perforated duodenal ulcer and cholelithiasis.

Inflammatory. In the primary group only 2 patients (Cases 27 and 32) gave a history of severe upper respiratory infections at the onset of their illness. One typical patient (Case 31) had a history of syphilis but developed the syndrome only after adequate treatment gave a serologically negative reaction. One patient (Case 20) had acute poliomyelitis at the age of 5 with a residual left foot-drop 31 years before the onset of amyotrophic lateral sclerosis. In the symptomatic group, there were a number which showed clinical signs and symptoms of inflammation of the nervous system.

Vascular. Despite the fact that we suspect a vascular etiology in some cases, and there is no doubt of this in certain bulbar types, few of our patients in the primary group showed evidence of vascular involvement. One (Case 32) had diabetes but without evidence of severe vascular disease. Another (Case 48) gave a history of thromboangiitis obliterans and coronary artery disease, and showed signs of generalized arteriosclerosis. Five others (Cases 29, 35, 40, 57, 58) showed clinical signs of marked generalized arteriosclerosis. In 2 of these, this was confirmed at necropsy. All had typical syndromes.

Toxic. None of the patients in the primary series showed any "toxic" manifestations, and, where suspicions were entertained, laboratory studies gave negative results. However, in the symptomatic group are recorded 2 cases following spinal anesthesia.

Trauma. This seems to us entirely fortuitous. In not a single instance was there anything to suggest an etiologic relationship between the trauma and amyotrophic lateral sclerosis.

Clinical Types. Tables 3 and 4 show the distribution according to "clinical types." Actually we feel that classification as to types adds little to the understanding of the problem, and merely describes localization in the nervous system. In our series the frequency of the various "clinical types" corresponds approximately to that reported by other authors.³

TABLE 3.—DISTRIBUTION OF 68 CASES ACCORDING TO CLINICAL TYPE

Type	Cases
Cervical	26
Bulbar	22
Quadriplegic	13
Lumbar	5
Hemiplegic	2
Total	68

Onset. The earliest manifestations of the disease recorded in our series are summarized in Table 4. The most frequent initial symptom was generally weakness of a hand or a leg, an arm or shoulder. Of

special interest was facial weakness as the initial symptom, and of the larynx as shown by impairment of the voice. The symptom of generalized weakness as a first manifestation occurred only in the bulbar group.

TABLE 4.—INITIAL MANIFESTATIONS OF AMYOTROPHIC LATERAL SCLEROSIS

<i>Lower extremities:</i>	Cases
Weakness, bilat.	9
Weakness, unilat.	8
Stiffness	1
Twitchings	1
Weakness and pain, bilat.	1
<i>Upper extremities:</i>	
Weakness, bilat.	3
Weakness, unilat.	25
Weakness and atrophy, bilat.	1
Weakness and atrophy, unilat.	8
Weakness and pain	4
<i>Other sites:</i>	
Hemiplegic weakness	1
Quadriplegic weakness	3
Marked generalized weakness	3
<i>Bulbar:</i>	
Voice changes	10
Dysphagia	7
Emotional instability	3
Dyspnea	2
Sialorrhea	2
Dryness of throat	2
Facial weakness	2
Pain in tongue	1
Pain in throat	1
Bitter taste	1
Nausea	1
Abdominal cramps	1

TABLE 5.—SIGNS OF PYRAMIDAL TRACT INVOLVEMENT

<i>Abdominal reflexes:</i>	Cases
Active	34
Weak	19
Absent	12
Absent, unilateral	3
<i>Plantar response:</i>	
Normal	22
Weak	9
Absent	6
<i>Extensor (Babinski):</i>	
Unilateral	12
Bilateral	19

Symptomatology. The signs naturally varied considerably according to the duration of the disease process. While, in general, weakness, atrophy and fibrillations tended to increase as the disease progressed, it was not uncommon to find marked weakness with little or no atrophy and fibrillations, or fairly marked fibrillations with only slight atrophy and weakness. In only one of our patients (Case 64) was there spasticity or an increase of tone in the upper extremities. In the lower extremities, especially in all the spinal types, spasticity or increased tone occurred frequently, but not invariably. A fairly common

observation was the presence of marked hyperreflexia with pathologic reflexes and little or no spasticity. Hyperactive jaw jerks were found in 14 cases, and, as was to be expected, most frequently in the bulbar type. Table 5 shows that diminution or absence of the abdominals occurred in less than half the cases. This is an important and well known fact. The Babinski sign, too, was found in less than half the number of cases.

Unusual Symptoms. Somewhat unusual symptoms were found rather frequently. Thirteen patients showed fairly marked emotional lability with frequent forced laughing and crying; this included 2 (Cases 47, 48) in whom euphoria was more or less constant. An oily face and a relatively fixed expression was seen in 2 patients (Cases 42, 55). We also observed unusual ocular signs. Three patients (Cases 24, 29, 58) had irregular pupils, and bilateral ptosis was present in 3 (Cases 25, 29, 60). Nystagmus was found in 2 (Cases 22, 52), and weakness of convergence in 1 (Case 19). Facial weakness occurred in 12 cases; this was bilateral in 5 and unilateral in 7. Loss of voice was the first symptom in 2 patients. Marked sialorrhea occurred in 6 patients. Dryness of the throat as a persistent complaint was present in 2 (Cases 42, 57). There was bilateral loss of taste in 1 patient (Case 16). One (Case 44) had several attacks of vertigo, 3 complained of hesitancy in urination, urgency and retention (Cases 24, 29, 58).

Sensory Symptoms and Signs. Generally neither pain nor sensory signs are associated with the syndrome, but 32 patients gave a history of both. These are summarized in Table 6. Pain, burning, tingling, numbness and other dysesthesias occurred at one time or another. In most instances they were transitory, in 9 cases they persisted throughout the course of the disease. One patient (Case 55) had an appendectomy performed because of abdominal pain. Objective sensory disturbances, namely, involvement of the peripheral nerves and of the posterior columns, have been reported by Wechsler, Brock and Weil⁶ and by Davison and Wechsler.²

TABLE 6.—SENSORY SYMPTOMS AND SIGNS IN AMYOTROPHIC LATERAL SCLEROSIS

<i>Subjective:</i>	Cases
Pain, numbness, burning, paresthesias	29
1. Preceding onset	5
2. At onset	3
3. During course	12
4. Throughout course	9
5. Abdominal pains	2
6. With onset of bulbar syndrome:	
Pain in throat	1
Pain in neck	1
Pain in tongue	1
<i>Objective:</i>	
1. Transitory loss of sensation—right median nerve	1
2. Hysterical hemi-sensory syndrome	1
3. Loss of vibratory sensation in lowers	1

Other Findings. Thorough general physical and extensive laboratory examinations were carried out on all patients. These included blood counts, urinalyses, blood chemistries, serologic studies, spinal fluid

examinations, gastric analyses, duodenal drainage, glucose and galactose tolerance tests, Roentgen rays of the skull, chest, large and small intestines, electrocardiograms, electroencephalograms and basal metabolisms. With the exception of the blood uric acid none of the findings showed any consistent deviation from the normal.⁷ Considering the fact that for the most part our patients were in the middle and older age groups, the relatively few cases of general physical disease are noteworthy. Although mental symptoms, namely, psychotic manifestations, are recorded in the literature,⁸ none of our patients in the primary group showed any. Spinal fluid studies showed no abnormalities in the primary cases, except for a not infrequent rise in protein, in 1 case as high as 84 mg. per 100 cc. Necropsy was performed in 11 cases. In all of these, the pathology was typical of amyotrophic lateral sclerosis. One case showed in addition evidence of old poliomyelitis.

TABLE 7.—CASES FOLLOWED UNTIL DEATH

No.	Type	Sex	Total duration (months)	Age at onset	Remarks
19	Bulbar	F	39	34	
20	Bulbar	F	8	36	
29	Bulbar	M	11	63	
35	Bulbar	M	22	64	
38	Bulbar	F	22	48	
42	Bulbar	M	36	42	Average duration, bulbar type: 20 months
47	Bulbar	M	21	35	
50	Bulbar	M	6	48	
52	Bulbar	M	23	53	
61	Bulbar	M	5	61	
30	Bulbar	M	26	36	
39	Bulbar	M	36	52	
23	Quadriplegic	M	25	23	
41	Quadriplegic	F	26	55	Average duration, quadriplegic type: 19 months
49	Quadriplegic	M	12	48	
58	Quadriplegic	F	13	56	
37	Lumbar	M	30	42	Average duration, lumbar type: 26.5 months
13	Lumbar	M	23	63	
40	Cervical	M	6	56	Average duration, cervical type: 14.7 months
44	Cervical	M	11	48	
8	Cervical	M	27	35	

Shortest duration, 5 months; longest duration, 39 months; average duration (22 cases), 19.6 months.

Course and Prognosis. Twenty-two of the 68 patients were followed until death. Table 7 summarizes some of the data on these cases. We wish to point out that while averages have some validity, they do not tell the whole truth. Thus, the average duration of the bulbar group was higher than that of the cervical. If, however, the 3 patients who survived 3 years are deducted, the average duration of the former drops below the latter. Furthermore, the larger number of deaths in the bulbar group shows that not only is the average duration less but the mortality is greater. Another point which is not evident from these averages is that while the average life expectancy is 2 years or less, quite a number of patients with amyotrophic lateral sclerosis live 3 or 4 or more years. This is true of all types, including the bulbar, although

in the main, those with initial involvement in the lumbar cord are apt to live the longest.

No spontaneous remissions were noted in any of our cases. In the vast majority the course was inexorably downhill to a fatal termination. Although we are not concerned here with therapy, we wish briefly to record a few observations on vitamin E administration without drawing any conclusions. All patients received adequate doses of vitamin E during the period of observation. Fifty-three showed not the slightest effect; 15 seemed to show some favorable response. Seven of the latter (Cases 1, 5, 6, 30, 32, 41, 54) showed a temporary improvement in one or more groups of symptoms, after which they continued their downward progression. Four (Cases 4, 10, 43, 56) showed what seemed to be an arrest, in that there has been no noticeable progression. Four others (Cases 14, 24, 55, 62) showed actual improvement in one or more signs, an improvement which has persisted during the period of observation. There have been no cures and no recoveries.

Symptomatic Amyotrophic Lateral Sclerosis. As already mentioned, the cases in the primary group were rather carefully selected to include only those that showed the typical combination of upper and lower motor neurone disease. However, a number showed a clinical picture identical with or closely resembling amyotrophic lateral sclerosis, but they seemed to be related to specific etiologic factors. These we designate as symptomatic.

Encephalomyelitis. Two patients presented clinically a picture of amyotrophic lateral sclerosis in the course of diffuse inflammatory disease of the nervous system. Wimmer¹⁰ long ago described cases of amyotrophic lateral sclerosis on the basis of encephalomyelitis. Although none of the cases included in the primary group gave a history of encephalitis, ocular signs occurred as unusual manifestations in 9 of the patients.

Case Studies. CASE 1. G.R. (298058), a 52 year old housewife began, 4 months before admission, with sudden onset of unconsciousness which lasted for 3 days, followed by stupor and a temperature of 105° F. for 1 week. She then had diplopia which lasted for 2 weeks, was unable to speak clearly, had difficulty in swallowing, and weakness of all 4 extremities. Gradually the weakness of the left side of the body receded while that of the right side of the body increased, and speech disturbance grew more pronounced. One month before admission, fibrillations of the right upper extremity were observed.

Examination showed right hemiparesis with spasticity and increased reflexes. There were fibrillary twitchings of both upper extremities with atrophy of the intrinsic muscles of the hands, the right greater than the left. The speech was nasal; there was paresis of the soft palate on the right side and the tongue deviated to the left. The right pupil was slightly larger than the left and there was slight ptosis and facial weakness on the right. There was also a right hemi-sensory syndrome. Lumbar puncture revealed 8 cells; the fluid was otherwise negative.

CASE 2. B.K. (441448-450292), a 49 year old woman was admitted to the hospital in May and in December of 1939. On the first admission, she showed a typical syndrome of disseminated encephalomyelitis. She began to recover and was discharged as improved. On the second admission, she showed, in addition to bilateral pyramidal tract signs, diffuse wasting of the muscles, especially of the hands, a picture which justifies the diagnosis of the syndrome of amyotrophic lateral sclerosis.

Syphilis. One of the cases included in the primary group gave a history that was definite for and showed pupillary signs that were characteristic of syphilis. Otherwise there was nothing to suggest an etiologic relation between lues and the typical picture of amyotrophic lateral sclerosis. In the following case the relationship seems to be present.

CASE 3. J.R. (341502), a 34 year old laborer, who contracted syphilis at the age of 27, developed bilateral wrist drop, which persisted unchanged despite adequate treatment. Examination revealed atrophy of the muscles of both shoulders, upper extremities and hands. There was generalized hyperreflexia with bilateral Babinski signs. The pupils were irregular and unequal; both reacted poorly to light and in accommodation. The blood Wassermann was negative.

Previous Acute Poliomyelitis. The relationship between poliomyelitis and amyotrophic lateral sclerosis has long been a matter of considerable interest.⁴ In the 68 primary cases, we have one patient who gave a history of poliomyelitis at the age of 5. At the age of 33, she developed typical amyotrophic lateral sclerosis. The following 3 cases, not included in the larger series, showed clinical syndromes resembling amyotrophic lateral sclerosis. Two of them had acute poliomyelitis in childhood, while the third showed, at necropsy, also the typical pathologic features of poliomyelitis without a previous history.

CASE 4. M.S., (457784), male, aged 41 had poliomyelitis at the age of 2 and residual flaccid paralysis of the left lower extremity. He was admitted to the hospital because of drawing sensations in both arms and heaviness of the hands. Examination showed generalized hyperreflexia (except in the paralyzed left lower extremity), absent abdominal reflexes, and a right Hoffmann sign. There was atrophy of the muscles of both hands and of the left leg, but no fibrillations. Later he developed difficulty in walking, more marked hyperreflexia, a questionable right Babinski sign, increased weakness and atrophy of the small muscles of both hands, and occasional fibrillations. The spinal fluid protein was 153 mg. per 100 cc. The syndrome had lasted 8 years.

CASE 5. N.W. (459052), a 40 year old woman gave a history of poliomyelitis in early childhood, with residual paralysis of the right leg. She was psychopathic and had repeated admissions to mental hospitals. At 38, right facial weakness and "trembling" of the hands appeared, and over a period of 2 years atrophy and fibrillations of both upper extremities and early bulbar involvement set in. On examination she showed motor involvement of the 5th, 7th, 9th, 10th, 11th and 12th cranial nerves, generalized atrophy and fibrillations, lively left knee jerk but otherwise depressed deep reflexes, and absent abdominals. The spinal fluid was normal.

Aside from the old poliomyelitis and the psychosis, the course and the widespread involvement suggested a virus infection. During this time there was one period when the clinical picture closely resembled amyotrophic lateral sclerosis.

CASE 6. H.B. (475237), a 51 year old tailor developed progressive weakness of the right hand and to a lesser extent of the left hand, followed by hoarseness. On examination he showed generalized weakness, most marked in the right upper extremity, atrophy of both deltoid and pectoral muscles, and questionable atrophy of the right forearm and right thenar eminence. There were fairly marked fibrillations in both upper extremities, especially in the deltoid and pectoral regions. The deep reflexes were slightly more active on the right, especially in the upper extremity; the abdominals were slightly diminished.

Six months later he began to have respiratory difficulty. He now showed a marked increase in the weakness of the upper extremities with pronounced atrophy and fibrillations, also weakness of the intercostal muscles, and weakness and atrophy of the thighs. The deep reflexes, except for the triceps jerks, were diminished; so were the abdominals. He died within 3 weeks. Necropsy revealed areas of hemorrhage and perivascular infiltration in the anterior portion of the spinal cord, most marked in the cervical region, with degenerative changes in the anterior horn cells. There were also some degenerative changes in the pyramidal tracts.

Toxic. Four of the patients in the primary group with typical pictures gave a history of exposure to toxic substances; namely, gasoline, lead and other heavy metals. However, in none were there toxic manifestations. In 2 patients a clinical picture resembling amyotrophic lateral sclerosis followed reasonably soon after spinal anesthesia to suggest a causal relationship.

CASE 7. C.D. (446493), a 45 year old woman developed gradually increasing stiffness of both legs 3 months after an appendectomy performed under spinal anesthesia. On examination she showed weakness and spasticity of the right leg with hyperreflexia in both lowers, absent abdominals and a right Babinski and Chaddock sign. The stiffness and weakness of her legs gradually progressed for 2 years. She then noticed weakness of her right hand, followed by bulbar symptoms. Two months before death, she had weakness of all 4 extremities with atrophies and fibrillations, and marked bulbar symptoms with atrophy and weakness of the tongue. The abdominals were absent, the deep reflexes were active in the uppers and depressed in the lowers. There was a hyperactive jaw jerk.

CASE 8. J.S. (423378), a 42 year old man received 3 spinal anesthetics for a multiple stage resection of a carcinoma of the rectum and sigmoid. While still in the hospital he began to complain of pain and weakness in the left arm and numbness of the left leg. Slowly, over a period of 4 years, he developed weakness of all 4 extremities and marked bulbar symptoms with bilateral pyramidal tract signs. During this period, he was admitted to the Johns Hopkins Hospital where a diagnosis of amyotrophic lateral sclerosis was made. His symptoms progressed steadily and he died 4 years and 3 months after the onset of his neurologic symptoms. Necropsy revealed central nervous system changes characteristic of amyotrophic lateral sclerosis.

Vascular. In none of the 68 cases included in the primary group was there conclusive evidence that vascular disease had direct etiologic relationship to the disease syndrome. The 5 cases which follow showed, we believe, such evidence. All but one ran a longer course than the primary cases of amyotrophic lateral sclerosis.

CASE 9. R.R. (425295), a 58 year old woman began with pain in her legs and her hands. Later she developed weakness and progressive atrophy. Examination revealed weakness of all 4 extremities with atrophy and fibrillations of the left leg and of both hands. She had a nasal, monotonous speech and some difficulty in swallowing. All the deep reflexes were markedly diminished, but the Babinski sign was present bilaterally. Besides generalized arteriosclerosis, she showed evidence of myocardial damage. She was observed for 2 years, during which she had two attacks of congestive failure.

CASE 10. L.W. (444014), a man aged 59, had had repeated hospital admissions over a period of 4 years because of peripheral vascular disease and arteriosclerotic heart disease. During this time he developed a combined anterior horn and pyramidal tract syndrome with atrophy of both hands, diminished abdominals, increased lower deep reflexes, and suggestive bilateral Babinski signs.

CASE 11. P.F. (468180), a diabetic 58 year old woman began with weakness of her left hand, followed by weakness and stiffness of the right hand and both

feet. On examination, she showed atrophy of both hands, but no fibrillations. The abdominal reflexes were absent, the deep reflexes in the lower extremities were hyperactive and there was a bilaterally positive Mendel-Bechterew sign. She had marked generalized arteriosclerosis.

CASE 12. J.O. (407557), a 60 year old woman, also a diabetic of long standing, began to have pain and weakness in all 4 extremities $2\frac{1}{2}$ years before admission. Examination revealed weakness, atrophy and fibrillations of all 4 extremities. There was generalized hyperreflexia, absent abdominals, and bilateral Babinski signs.

CASE 13. M.H. (401480), a 48 year old man was known to have hypertension for 2 years. One year before admission to the hospital he began to have steadily progressing weakness of the left lower extremity. On examination he showed weakness of both lower extremities with some atrophy and fibrillations of both thighs. There was some weakness of the left hand. The deep reflexes were hyperactive, the abdominals were diminished, and there was bilateral Babinski sign with ankle clonus.

Comments. As stated in the introduction, we purposely excluded cases of progressive spinal muscular atrophy and lateral sclerosis, and for the following reasons. Amyotrophic lateral sclerosis is a disease of adult life and of middle and old age. We recorded only 1 rare instance below 20 and only 2 between 20 and 30. Progressive spinal atrophy is common in young people and lateral sclerosis, even excluding the familial group, also occurs at all ages. We realize, of course, that many cases beginning as "pure" pyramidal tract affections slowly or rapidly go over into multiple sclerosis, amyotrophic lateral sclerosis or other syndromes, but we are not here concerned with transition cases. Lateral sclerosis and progressive muscular atrophy are very slowly progressive conditions. Patients with either disease live for years and years, up to 20 and 30 or longer after the initial signs or symptoms appear. Amyotrophic lateral sclerosis is fairly rapidly progressive, and most patients die within 2 to 3 years. There are exceptions, and like others we have seen patients who survived 5 or 6 years, but in the very vast majority of cases the statement holds that we are dealing with a subacute and invariably fatal syndrome. It is worthy of comment that those patients with amyotrophic lateral sclerosis survive longest in whom the pyramidal tract signs predominate, particularly if the lower extremities are first or largely affected; while those die soonest in whom the atrophy predominates, especially in the cervical and bulbar regions. It would seem, therefore, that we are dealing with 3 different conditions of unknown etiology; that there is some selective affinity of the pathogenic agent for different structures in the 3 syndromes; that if the selectivity is limited either to the anterior horn cells and their nuclear homologues of the cerebral nerves or to the pyramidal pathways the result is a slowly progressive one; and that if by chance the old and new motor systems are simultaneously affected, the progress is rapid and the disease invariably fatal.

The conviction has gradually grown on us that amyotrophic lateral sclerosis is not one disease entity. It is true that the majority of cases are so-called typical or, as we should prefer to designate them, *primary*; but there are many which seem to us to be *symptomatic*. The first group appears to be the result of a "degenerative" process. There is some inferential evidence that deficiency plays a rôle in some cases of the primary group. The pathologic picture bears close resemblance to

that seen in known deficiency diseases. The selectivity of involvement points in that direction. The isolated instances in which vitamins seem to play a rôle is another consideration. The relentless and uniformly progressive course is also suggestive. In any case the suspicion is very strong that the primary group represents one syndrome. On the other hand, there is no doubt, from our material and from numerous instances recorded by others, that inflammation of the nervous system can give rise to a syndrome of anterior horn and pyramidal tract disease. This is attested by clinical histories and by spinal fluid changes with increased cells and protein. The increase in protein alone is not altogether conclusive as one occasionally observes the rise in cases which appear to be primary. Third, there are few but definite instances of amyotrophic lateral sclerosis which are unquestionably the result of vascular disease. They are apt to be cases which begin with bulbar signs and symptoms, possibly also at first pseudobulbar, in whom the pyramidal tract signs though present are not very pronounced. They occur mainly in persons of advanced years. Finally, to these 3 syndromes one may possibly add a fourth consisting of 2 cases which followed spinal anesthesia. They may be designated as toxic, and there may be other instances, but the proof of toxic factors is otherwise lacking.

The statement has been made that the progress of fibrillations varies with the progress of the disease; that is, the more rapid and widespread the fibrillations the more rapidly fatal the disease. In our experience this is only partly true. We have seen instances where fibrillations ceased and the disease progressed rapidly nonetheless; others in whom fibrillations were comparatively rare throughout a fairly rapid course; still others which showed marked fibrillations with a protracted course. We have also observed marked atrophies with rare fibrillations and widespread fibrillations with moderate atrophies. One cannot therefore always assert the parallelism nor prognosticate the course of the illness from the fibrillations alone.

Of interest in our cases was the comparatively frequent onset with bulbar signs and symptoms. These, and pseudobulbar signs, generally come late, but the syndrome in several of our patients began with loss of voice, difficulty in speaking, facial paralysis, distressing sialorrhea, and the emotional disturbances seen in pseudobulbar palsy. All of the patients did badly. Not easily explained were the few cases with pain at the onset of the illness. While rare instances of amyotrophic lateral sclerosis with objective sensory signs are recorded in the literature, subjective sensory disturbances may be complained of. In our cases the pain generally ceased as the disease progressed. Whereas emotional disturbances were comparatively frequent, no patient in our series showed either minor or major psychotic disturbances.

Finally we would confirm what is fairly well known, the want of parallelism between hyperactive deep reflexes, the Babinski sign and absent abdominal reflexes. The first are invariably present and obviously point to pyramidal tract involvement; the last two are not always found but their absence is no evidence against involvement. The explanation for this is not clear.

Conclusions. 1. We have recorded the clinical manifestations of 81 cases of amyotrophic lateral sclerosis, studied the clinical types, the various modes of onset, the unusual manifestations, possible precipitating factors, clinical variants, and the course of the disease. In general we would suggest the division of cases into *primary* and *symptomatic* groups.

2. It seems that amyotrophic lateral sclerosis is not one disease entity dependent upon one etiologic factor, but a syndrome of varying etiology. The largest group consists of so-called degenerative cases, some of which may possibly be the result of selective deficiency. Smaller groups may be the result of inflammatory processes or vascular changes. An even smaller group may possibly be toxic in nature.

3. From our own observations and those of others, the conclusion is justified that amyotrophic lateral sclerosis, progressive muscular atrophy and uncomplicated lateral sclerosis are three different entities. The first is comparatively rapidly progressive and invariably fatal, the other two are very chronic and last years and years.

4. While the intensity and extent of fibrillations often reflect the gravity of the disease there is no constant parallelism between them and one cannot prognosticate on the basis of fibrillations alone.

5. In many cases pseudobulbar manifestations may signalize the onset of amyotrophic lateral sclerosis.

6. Our studies confirm the want of parallelism between presence of active deep reflexes, absence of abdominal reflexes and a Babinski sign, despite involvement of the pyramidal tracts. The first always is present, the second two may or may not be.

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THE ELECTROCARDIOGRAPHIC CHANGES FOLLOWING ARTIFICIAL HYPERPYREXIA*

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MUCH speculation has existed regarding the significance of electrocardiographic (ECG) changes seen after artificially induced hyper-

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pyrexia. It is the purpose of this work (1) to describe ECG changes of a type not mentioned in the literature following hyperpyrexia, and (2) to attempt an explanation of them.

Vesell and Biernan,¹² in 1936, reported the detailed ECG changes in 10 patients subjected to artificial hyperpyrexia, and stated that the alterations of the individual waves were not uniform. They found that P and T waves were almost as frequently increased as decreased in size, and that the RT level usually was depressed, never elevated. They attached special significance to the development of a prominent Q-3 in one instance. They felt that the changes probably were due to "reflexes, tachycardia, local cardiac and general chemical and physiologic alterations." They concluded that none of the changes were permanent, and that it could not be inferred that fever produced any harmful effect upon the heart.

At the same time, Simpson¹⁰ stated that the post-fever ECG showed only minor transient alterations. When questioned regarding the relationship of these changes to the degree of alkalosis, he replied that some degree of alkalosis was present uniformly in patients subjected to high, sustained, artificial fever.

Neymann,⁹ in 1938, stated that the ECG showed increased rate, frequently with shortening of the PR interval. He added that the T wave usually was changed—frequently obliterated—and that the changes might last several days, but that fever has no permanent effect on the normal heart.

In 1941, Dawber³ reported a case of "coronary thrombosis," following hyperthermy, in a 21 year old patient. The first ECG was taken 5 days after the acute attack of sharp substernal pain, accompanied by vomiting, and showed inverted T waves in leads II and III, and diphasic (beginning inversion) in lead I. Right axis deviation was present. There was no elevation of the S-T segments; if anything, there was a slight depression. There were no chest leads taken, and there was no record of the erythrocyte sedimentation rate or of the white cell count. The patient's temperature was not mentioned. A second tracing taken 13 days later (again without chest leads) showed inversion of T-1 with an upright T wave in leads II and III. Tracings taken approximately 2 and 4 weeks later showed no significant changes. A final tracing, taken 4 months after the first one, was normal. This was the only tracing in which a chest lead was taken. At this time (4 months after attack) the sedimentation rate was 2 mm. and the white cell count was 8600 with a normal differential count.

During the same year, Knies⁶ reported the ECG changes observed during 52 treatments of 20 patients. He found the changes to be insignificant with none suggestive of cardiac damage. He agreed in general with the observations of Vesell and Bierman, and concluded that the changes were the result of physiologic processes incidental to the temperature increase regardless of its mode of induction.

In 1943, Turville and Fetter¹¹ reported on the ECG changes following artificial fever in 13 patients. They were unable to correlate the changes with the age of the patient, the height of the fever, or the

cardiac rate. Their observed changes apparently were similar to those previously reported, but they felt that the changes were more significant and should call for closer watching of the patient with termination of the fever at the earliest sign of cardiovascular failure.*

Procedure. All fevers were induced by means of a cabinet employing the principle of hot air whose relative humidity ranges from 85 to 95%.

Each patient received a *conditioning fever* during which the body temperature was elevated to 101° F. for 30 minutes. Such fever was administered to acquaint the patient with the technique of the forthcoming therapeutic fever, and to give him the benefit of increased blood volume, which is said to result from this procedure.⁷ In the administration of *therapeutic fevers*, an attempt was made to maintain the patient at between 105° to 107° F. for a period of 5 to 10 hours. These objectives were not attained in all cases, patients being removed from the cabinet for various reasons.

In an attempt to maintain normal physiologic relationships at the elevated temperature, all patients received fluids up to 500 cc. per hour, continuous oxygen, and, when necessary, 50% dextrose.

Electrocardiograms were taken routinely on all patients before and after fever therapy to determine the effect, if any, of this procedure. Tracings also were taken following conditioning fevers, since these offered an opportunity to study the effect of fevers differing in duration and intensity.

In several instances, tracings were taken at regular intervals throughout the fever, but this was discontinued because it seriously interfered with the treatment. It is necessary to maintain a high degree of humidity in the fever cabinet, and this can not be done if the cabinet is frequently opened. Furthermore, this work already had been performed and reported by Knies,⁶ and a repetition seemed unnecessary.

The series of 86 patients, with a total of 118 sessions of fever.[†] Of these, 80 were therapeutic fevers, and 38 conditioning. In the case of the therapeutic fevers, the height and duration are given with the data.

The data are found in Table 1. Briefly, it was found that of the 80 cardiograms following therapeutic fever, 64 showed changes of an insignificant nature, 7 showed significant changes, and 9 showed no change whatever from the pre-fever tracing.[‡] Of the tracings taken following conditioning fever, 21 showed no change, 16 showed insignificant changes, and none showed changes of any significance.

Insignificant Electrocardiographic Changes. *Character.* Previous workers¹² have described in detail§ the post-fever changes in the individual components of the ECG. It was desired to check these findings. Consequently, a series of 27 cases of those showing insignificant changes was charted and analyzed in detail. The result of this analysis is in Table 2.

* While I am in full agreement with the conclusion that patients should be removed from the fever cabinet at the earliest sign of cardiovascular failure, I fail to see any direct relationship between this condition and the ECG changes as described.

† In the case of multiple therapeutic fevers in a single patient, only the first was included for statistical purposes except in a few cases where the other sessions produced ECG changes of different significance.

‡ Although 7 cases are listed as showing significant changes, it will be seen that 9 are discussed. This is because one (5177) showed insignificant changes in his post-fever tracing, developing significant changes on the following day. The other (6673) was studied just prior to publication and was not listed.

§ It is felt that the work of Vesell and Bierman, in which amplitude is measured down to 0.1 mm. and time down to 0.01 sec., attempts to obtain an unwarranted degree of accuracy.

TABLE 1.—DATA REGARDING CASES UNDERGOING HYPERTYREXIA

No.	Age	ECG	Rate	CO ₂	Liver	Fever			Vomit	Psyche	Shock	Short fever		Remarks
						Time (hrs.)	Degree	ECG				Rate	ECG	
5801	20	3	60-110	8	106.8	85-110	1	Plus 2 changes 4 hr. post-fever; rate then 83.
5128	19	n	85-110	44-36	..	10	106.8	
5413	26	3	85-115	4½	106.8	
4950	28	n	75-135	8	106.5	..	v	
5176	21	1	75-115	52	..	5	106.8	..	v	DN	..	65-80	2	Normal 2 hr. post-fever; rate 91.
5355	24	2	65-100	40	..	10	106.8	
4941	20	2	65-110	8	106.5	90-90	n	Removed—fast pulse, low b.p.
5079	20	2	90-110	46	..	8	106.8	100-115	n	
4743	42	n	100-105	..	SCJ	2	103.3	65-100	n	P-2 sharp, T-4 flat; normal in 3 days. Stopped: b.p. 90/60; inverted T-4.
5205	22	1	65-85	54-46	..	8	106.8	..	v	D	
5888	25	2	80-110	8	106.8	S	70-83	n	Stormy 2 hr. induction; cyanotic; restless; tachycardia.
5318	31	s	70-90	51-40	..	6	106.8	
5139	19	n	60-100	56-54	SCJ	8½	106.8	D	..	70-88	n	
5077	20	n	70-95	42	..	10	106.8	70-92	1	
4954	27	1	70-110	..	J	10	106.8	D	..	75-83	n	SI elevation of ST-2 and 3; 4 hr. post-fever.
5238	26	1	75-115	6½	106.8	SPR	75-85	n	
5081	25	2	75-110	..	J	9	106.8	T	..	60-94	n	1 week later, ST-T normal, but P waves entirely changed.
5085	24	1	60-130	4	106.8	
5865	21	1	70-110	5½	106.8	Slight cyanosis.
4385	23	2	55-110	5	105.0	75-110	2	
5193	24	..	85-115	46	..	9½	106.8	SPR	85-80	n	Shift to right axis deviation.
5148	20	2	85-100	50-36	..	9	106.8	PR	
5175	28	1	75-110	8	106.5	..	v	
4907	25	4	
5166	19	n	65-110	..	SCJ	5½	106.8	..	v	..	S	65-90	n	Slight cyanosis.
5785	19	1	70-110	43	..	9½	106.8	..	v	70-90	n	
4742	40	1	80-125	10	106.8	..	v	D	..	80-112	1	
5135	29	90-85	n	
5317	23	2	85-125	57-42	SCJ	7½	106.8	80-105	n	1 week later, ST-T normal, but P waves entirely changed.
5082	35	2	85-115	10	106.8	85-90	n	
5281	49	2	75-105	1½	105.0	85-108	1	Shift to right axis deviation.
5102	23	2	85-145	46-40	..	5	106.8	..	v	100-108	n	
5968	23	3	100-125	5	106.8	70-90	n	
5057	25	n	80-95	..	SCJ	10	106.8	
5083	25	4	70-90	..	SCJ	10	106.8	..	v	D	..	75-83	n	Shift to right axis deviation.
4939	23	1	90-105	4½	106.8	60-92	n	
5055	26	1	100-100	52	J	9	106.8	..	v	60-73	n	
5771	35	2	75-105	61-44	SCJ	5	106.8	TD	..	65-112	2	
5236	19	2	80-125	56-38	SCJ	4½	106.8	Shift to right axis deviation.
5127	20	1	60-110	44	J	10	106.8	
5087	27	2	60-115	10	106.8	..	v	
5030	28	2	65-105	10	106.8	..	v	

It may be stated, in general, that about one-half of the cases showed increased amplitude of the P wave, with a maximum increase of 1 mm. There were very few cases in which the P wave was decreased in amplitude. In the majority of cases, there was some diminution of the voltage of the QRS complex, but this never exceeded 1 mm. in the limb leads. The S-T segment was depressed in but 10 of the cases (Vesell and Bierman¹² found the R-T phase depressed in "almost every case") and was elevated in none. The majority showed T waves whose amplitude was decreased as much as 4 mm. in the limb leads, but in several cases the amplitude was increased.

TABLE 2.—DATA REGARDING ELECTROCARDIOGRAPHIC CHANGES IN 70 TRACINGS TAKEN DURING 43 FEVER SESSIONS

Number of patients, 27; number of fever sessions, 43; number of electrocardiograms, 70

	No change	Increase	Maximum increase (mm.)		Maximum decrease (mm.)
P wave*	18	20	1	4	1
R wave	11	9	5†	26	5†
S-T segment	33	0	0	10	1
T wave	13	4	1‡	26	4
Bazett's "K"	1	33	0.096§	9	0.065§

* One case questionable, as P wave was superimposed on T wave of preceding complex.

† In lead IV-F, the maximum increase was 20 mm. and the maximum decrease was 9 mm.

‡ Maximum increase of 5 mm. in lead IV-F.

§ Average increase 0.037; average decrease 0.021.

The one measurement apparently disregarded by previous workers was the Q-T interval. This is the measurement of the electrical systole and is correlated with the square root of the cycle length. The value obtained by means of this correlation is known as Bazett's "K."* This value was unchanged in 1 case, was decreased in 9, but was increased in 33. Furthermore, it is seen that the average increase was 0.037 while the average decrease was but 0.021. This points toward this figure as being one of the most constant changes yet described in the ECG following artificial fever. Moreover, this change cannot be ascribed to the rate, as this factor already has been accounted for in the formula.

It must be reëmphasized that none of the changes described are specific following fever therapy; that none are constant in the degree or direction of the change; and that, generally speaking, they are of no significance.

Classification. Broadly speaking, the ECG changes following fever therapy fall into 3 groups showing: (1) No change; (2) no significant change; and (3) significant change. In the section dealing with the insignificant changes, it was shown that these changes were not constant in direction and amplitude. For statistical purposes, it is necessary to devise a more simple classification of these changes rather than to list separately the effects upon each complex.

$$* \text{ Bazett's "K" } = \frac{\text{Systole}}{\sqrt{\text{Length of cycle}}}$$

The following gradation was found to be satisfactory: N—no change; 1—slight lowering of voltage of T waves in leads I, II, or IV; 2—moderate lowering of voltage of T waves in leads I, II, or IV; 3—marked lowering of voltage of T waves in leads I, II, or IV; 4—1, 2, or 3, with depression of the ST segment; S—significant change.

In this scheme, any inversion of the T wave, except in lead III alone, was considered to be abnormal and was not classed in the insignificant changes.

It should be remembered that grades 1 to 4 consist of *insignificant* changes and that the grouping is merely a means of convenience rather than an attempt to reach unwarranted conclusions.

Jaundice. ECG changes in gall bladder disease have been described.⁴ It is possible that these changes are due to an abnormal amount of bile salts in the blood stream. Knowing that jaundice can be a complication of hyperthermia, it was desired to determine if this was a factor in the production of the ECG changes following fever.

Those patients showing hepatic involvement were divided into two general classes: (1) jaundice; and (2) subclinical jaundice, which consisted of those with increased serum bilirubin in amount insufficient to cause clinical jaundice.

The data in Table 1 show that of the 5 patients with jaundice, none showed greater than grade 2 insignificant changes in the cardiogram. It is of interest that Patient 5055 had severe hepatic damage, yet his cardiogram showed only grade 1 insignificant changes.

Of the 8 patients with subclinical jaundice, 2 showed no change, 1 showed grade 4 changes, the remainder varying between grades 1 and 2. None showed changes of any significance.

These data show that liver damage, as indicated by increased serum bilirubin, was not a factor in the production of the ECG changes following fever therapy in this series of cases.

Alkali Reserve. Simpson¹⁰ stated that some degree of alkalosis was present uniformly in patients subjected to high, sustained, artificial fever. Barker¹ inferred that this might be a factor in the production of ECG changes.

In 11 cases, the carbon dioxide combining-power was determined as a routine measure before and after fever therapy (Table 1). In every case this value was lowered. Of these, 2 cases showed no changes in the cardiogram, and 1 showed significant changes. Of the remaining 8, 4 showed grade 1, 3 grade 2, and 1 grade 3 changes.

In 10 cases, a post-fever carbon dioxide combining-power was determined because it was felt that there might be some derangement of the alkali reserve. In each instance, the result either was normal or indicated a diminution of the alkali reserve, the values ranging from 52 to 38 volumes %. The cardiographic changes ranged from none to grade 2.

While these data do not indicate the presence of acidosis, they do show that alkalosis was not a causative factor of the cardiographic changes in this series of cases.

The Effect of Rate and Fever. STATISTICAL STUDY* *Rate.* With little or no change in rate, the possibility of there being no ECG change is great. With changes between 10 and 20 beats per minute, the possibility is more than 2 to 1 of there being changes, and when the increase is more than 20 beats per minute, the odds are overwhelming in favor of there being changes.

Fever. In the case of conditioning fevers, one may or may not find changes; the possibility of there being no change being slightly greater. In all of the therapeutic fevers, however, changes are almost always present.

These findings support the previously expressed opinion that increased cardiac rate is a major, but not the sole, factor in the production of the ECG changes following fever.

Significant ECG Changes. The following cases were admitted to the hospital for the purpose of receiving hyperpyrexia. All had drug-resistant gonorrheal urethritis except Case 5318, who had gonorrheal arthritis. Each had a cardiac examination, including ECG, prior to fever. None showed any abnormality.

CASE 5177 (Fig. 1). This 28 year old patient gave a history of rheumatic fever. On April 27, he received 8 hours of therapeutic fever at 106.8° F. Although fatigued, his general condition was said to be good. His blood pressure was 106/70, and his post-fever ECG showed only insignificant changes. Several hours later his blood pressure fell to 86/60. At about 2 A.M. on April 28, following 250 cc. of a plasma infusion, he developed fever and chill. The chill lasted about 15 minutes, and the blood pressure was 102/80. At 7 A.M., the blood pressure was 80/60, and at 11 A.M., the patient complained of severe substernal burning and pressure. At 2 P.M., the blood pressure was 98/70, the heart sounds were distant, and the ECG showed marked elevation of ST-4.† On April 29, his blood pressure was 100/70, and he was comfortable while receiving accepted treatment for myocardial infarction. His white cell count was 11,250 with 92% polys and his sedimentation rate was 19 mm. In the morning of the same day his ECG showed a marked return to normal, but by evening, the S-T segment was abnormally elevated in lead CR-6. For the next few days, his clinical condition was essentially unchanged; the blood pressure ranging between 100/80 and 120/60. Examination of the ocular fundi revealed no evidence of old or recent hemorrhage. On May 9, the patient complained of precordial pain, a diastolic murmur was heard over the aortic area, a third sound was heard over the apex, and a Roentgen ray revealed enlargement of the left ventricle. The ECG, which in the meantime had shown inverted T waves in the limb leads and gradual regression of the inverted T in CR-6, showed marked inversion of the T wave in IV-F, CR-4, and CR-6. His white cell count was 7400 with a normal differential, but his sedimentation rate remained elevated at 17 mm. On May 22 a Roentgen ray showed decrease in the size of the left ventricle, and there were no murmurs present. Because of this, and the fact that no murmurs have been heard since, it is felt that the findings of May 9 were due to dilatation of the left ventricle. From this date on, improvement was gradual but progressive. By early July, his ECG and sedimentation rate had returned to normal.

It is obvious that this patient suffered severe myocardial damage, the cause of which is questionable.

* These results are based on the data of the entire series of cases. "Significant" changes are included for completeness only, it being realized that this group is entirely too small for the purpose of statistical comparison.

† Throughout this paper, "ST-4" and "T-4" refer to complexes in lead IV-F.

It is well known that hyperpyrexia is capable of causing multiple small hemorrhages in various organs.^{5,8} With the marked elevation of ST-4, seen in the ECG of April 28, it was felt that the underlying pathology might be a small subepicardial hemorrhage. While this cannot be ruled out, the course of subsequent events makes it improbable.

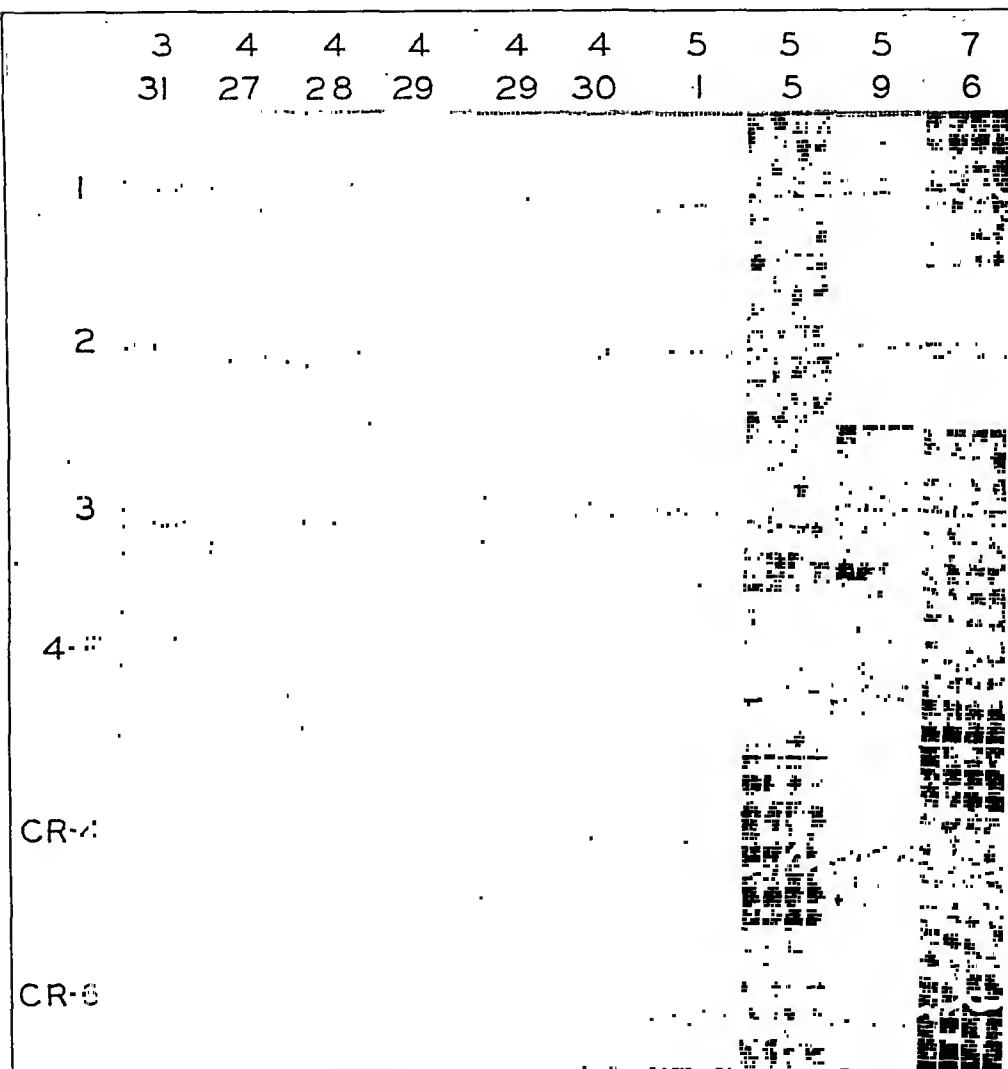


FIG. 1.—Electrocardiograms of Case 5177, showing acute change on April 28 with progression up to May 1; some return toward normal by May 5; and acute recurrence of changes on May 9.

Despite the fact that the T waves in the limb leads and the ST-4 suggest epicardial, rather than myocardial, involvement, study of the entire series of tracings is more indicative of coronary thrombosis, because of the sudden change seen in the tracing of May 9. Had the original condition been due to hemorrhage, one would expect the ECG

gradually to return to normal. In coronary thrombosis, however, it is not infrequent to have an extension of the thrombus, causing changes similar to these. Furthermore, it would be unusual to find the hemorrhage following fever involving a single organ. In this case there was no evidence of hemorrhage at any place in the body. Also, blood taken from the patient's arm on April 28 coagulated immediately.

CASE 5956. This 22 year old patient received 8 hours of therapeutic fever at 106.8° F. during the night of May 29-30, and apparently reacted in a normal manner. Following fever he had no complaints except headache and mild lumbar pain. The routine post-fever ECG showed low voltage T waves in the limb leads and an inverted T-4. His blood pressure stayed in the vicinity of 100/65, and the sedimentation rate was 2 mm. The white cell count was 6400 with a normal differential. On May 31, the tracing showed limb leads which were less abnormal and T-4 which was less inverted than previously. The CR leads were normal but ST-4 was elevated. The blood pressure averaged 95/60. On June 1, T-4 was entirely upright, but showed slight notching of its descending limb.

Subsequent course showed gradual return of the blood pressure and ECG to normal. The patient's temperature and white cell count were normal throughout the entire illness. The sedimentation rate was 2 mm. on June 14, but rose to 15 mm. on June 21. The patient was asymptomatic except for headache, and was about to be discharged from the hospital when, on July 8, 39 days after fever therapy, he developed, for the first time, precordial pain. This was accompanied by an elevation of ST-4 with inversion of T-4, a white cell count of 5300, and a sedimentation rate of 16 mm. The pain was relieved by oxygen. On July 9, the ECG was normal except for notching of T-4. His course from there on showed gradual improvement.

Because of this change that occurred on July 8, it is felt that this also is a case of myocardial infarction, probably on the basis of thrombosis of a small branch of a coronary artery.

CASE 5883. This 23 year old patient had rheumatic fever at age 15 with frequent recurrences since. He had no symptoms at any time referable to the cardiovascular system, and his pre-fever examination was normal. An ECG was normal, although the R wave in lead IV-F was only 2 mm. He received 10 hours of therapeutic fever at 106.8° F. on May 19. Following this, he was moderately fatigued, and his blood pressure was 100/60-0. The heart sounds were distant but there was no evidence of pericardial effusion. Twenty-five minutes after removal from cabinet, he complained of sharp pain in the left lower chest. This pain was relieved by eructation of a large amount of gas. His ECG showed lower voltage and diphasic T-4. About 3 hours later, his blood pressure was 100/40, he again complained of chest pain, and he vomited 300 cc. of light brown fluid. At midnight, the patient was complaining of dyspnea. Throughout the night his blood pressure ranged between 80/50 and 95/55. On May 20, his ECG showed definite cove-shaped inversion of the T waves in leads IV-F, CR-2 and CR-4. The patient was comfortable except for a dull, squeezing, precordial pain which did not radiate. The blood pressure was 96/60, the white cell count was 8850 with normal differential, and the sedimentation rate was 3 mm. His condition remained unchanged throughout the day, and his pain was relieved by oxygen and morphine. On the morning of May 21, he complained of several attacks during the night when his oxygen mask had slipped off, but his general condition remained the same. On May 22, he still complained of dyspnea and precordial pain, but the heart sounds were of better quality, and the blood pressure was 100/60. His ECG showed return toward normal. The T waves, which had been inverted, were now diphasic. His condition showed gradual but definite improvement. Subse-

quent white cell count and sedimentation rate were normal, and the ECG approximated the pre-fever normal on July 6.

On July 15, 56 days following fever therapy, while gradually increasing his physical activity prior to discharge from the hospital, he again developed precordial pain. His ECG on the following day showed slight elevation of ST-4, with inverted T-4. The T wave in lead CR-2 also was inverted. The patient was afebrile and his white cell count and erythrocyte sedimentation rate were normal. His symptoms subsided while he was kept at absolute bed rest. On July 19, the ECG again had returned to its pre-fever normal.

From this point on, improvement was gradual but definite.

The sudden change on July 18, as in Case 5956, leads to the conclusion that the entire syndrome was due to occlusion of a small coronary artery.

CASE 5318. This 31 year old patient was given 6 hours of therapeutic fever at 106.8° F. on April 5. This treatment was discontinued because the blood pressure fell, and stayed at 90/60 and below. The post-fever tracing showed inversion of the T wave in lead IV-F with a QRS complex of entirely different configuration. A tracing taken several days later was similar to that taken prior to the fever.

On April 30, he received a 5-hour fever to which he responded well. There were no obvious complications, and no ECG was taken.

On May 26, he received 3 hours at 106.5° F. This treatment was discontinued because of cardiovascular depression with blood pressure readings of 86/60 and 90/60. He was given plasma which caused a reaction. An ECG again showed inverted T wave in lead IV-F.

Despite the fact that the QRS complexes in lead IV-F differed in contour from time to time in the different tracings, it can be stated positively that the electrode was placed near enough to the same position to make them comparable.

Throughout the entire course of hospitalization, the patient never complained of precordial pain. He had a total of 13 white cell counts, all of which were normal. His sedimentation rate was 26 mm. on May 24, and 24 mm. on June 11.

CASE 6046 (Fig. 2). This 32 year old patient received an 8-hour therapeutic fever at 106.8° F. on May 29. At one time during the fever, his remarks were irrational, and at the end of the fever he was fatigued, but his general condition was said to be good. Following fever, he had no complaints, and his blood pressure stayed at about 120/80; but his ECG showed flattening of all T waves, depression of ST-2, and inversion of T-4. On May 31, his tracing had returned to normal.

His white cell count was normal on several occasions, and his sedimentation rate on June 1 was 2 mm.

CASE 5461. This 25 year old patient had no abnormal physical signs except for a soft, grade 1, systolic murmur at the apex; in all probability a functional murmur. Therapeutic fever was attempted on May 13, but discontinued after 1 hour at 106.8° F. because the patient became hysterical and attempted to break out of the cabinet. His blood pressure remained perfectly normal, and he had no symptoms referable to the cardiovascular system. His post-fever ECG showed inversion of T-1, diphasic T-4, and low voltage T waves with depressed ST segments in leads II and III. A tracing taken on May 17 showed return to normal except for slight elevation of ST-4 and absent S-4. On June 7, a tracing was entirely normal.

CASE 6673. This 24 year old patient received an 8-hour therapeutic fever at 106.2° F. on June 26. There were no complications, and his condition following fever was considered to be excellent. There were no cardiac symptoms at any time, and his blood pressure remained in the vicinity of 110/80 during and following the fever. His post-fever ECG showed inverted T waves

with depressed ST segments in leads II and III, with a small diphasic T-1, and notched T-4. A tracing taken June 30 showed complete return to normal.

Several weeks later, following supervised exercise, his ECG showed tachycardia with depression of ST in leads II and III and lowering of voltage, but no inversion, of the T waves.

CASE 5880. This 22 year old patient received 6 hours of therapeutic fever at 106.8° F. on May 20. His post-fever ECG showed inverted T waves in leads II and III. The patient had no complaints, and his blood pressure remained at about 110/80. On two occasions followed fever, his white cell count and differential were normal. His ECG was normal on May 22.

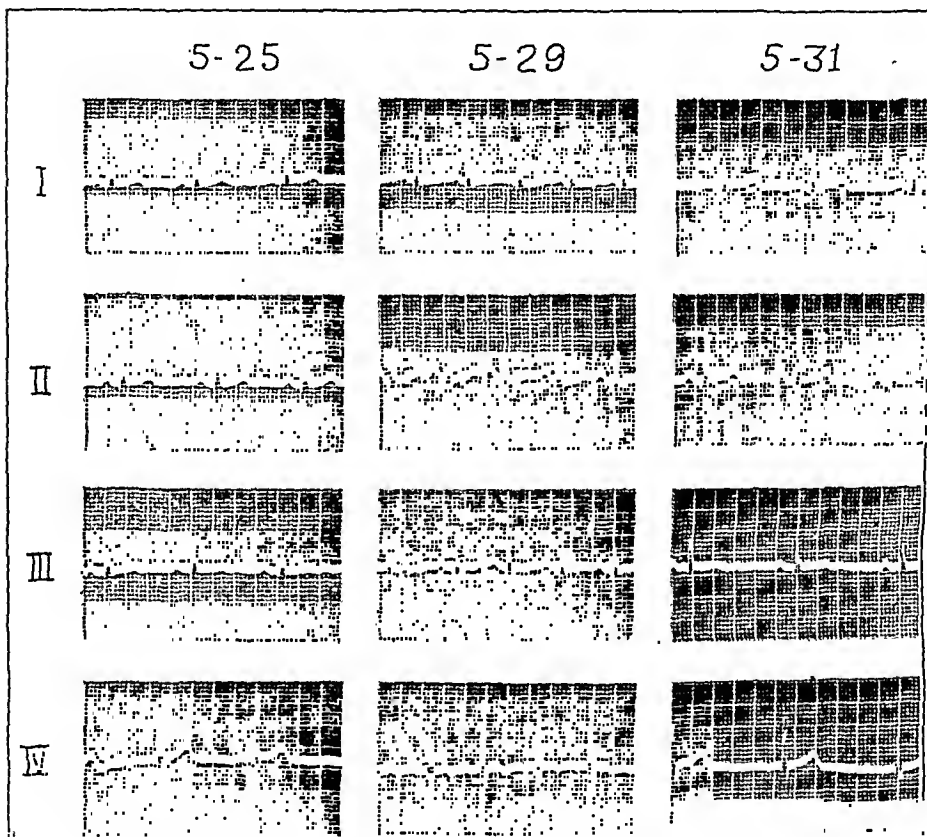


FIG. 2.—Electrocardiograms of Case 6046 showing typical "significant" post-fever changes.

Several weeks following fever, the patient was given supervised exercise, tracings being taken after light and moderate exertion. Tachycardia was the only change in the ECG.

CASE 5881 (Fig. 3). This 22 year old patient was given fever therapy on May 21. During induction of fever, he complained of weakness. Because of cyanosis and a blood pressure of 95/50, treatment was terminated after 1 hour and 20 minutes. At that time he complained of a severe pain in the right renal region, and an ECG showed the T waves to be small and inverted in leads II and III, while in the same leads the P waves were large and pointed. A tracing taken 1 hour later showed T-2 to be small but upright; the P waves remaining unchanged. Lead CR-2 (not shown) showed an unusually tall T wave. The patient's blood pressure rose to 110/75, and stayed at about this level. A tracing taken the following day was normal except for the large

T wave in CR-2. Tracings were retaken several times, and this finding remained constant. Therefore, it was felt to be normal for the individual. On two occasions following fever, his white cell count and differential were normal.

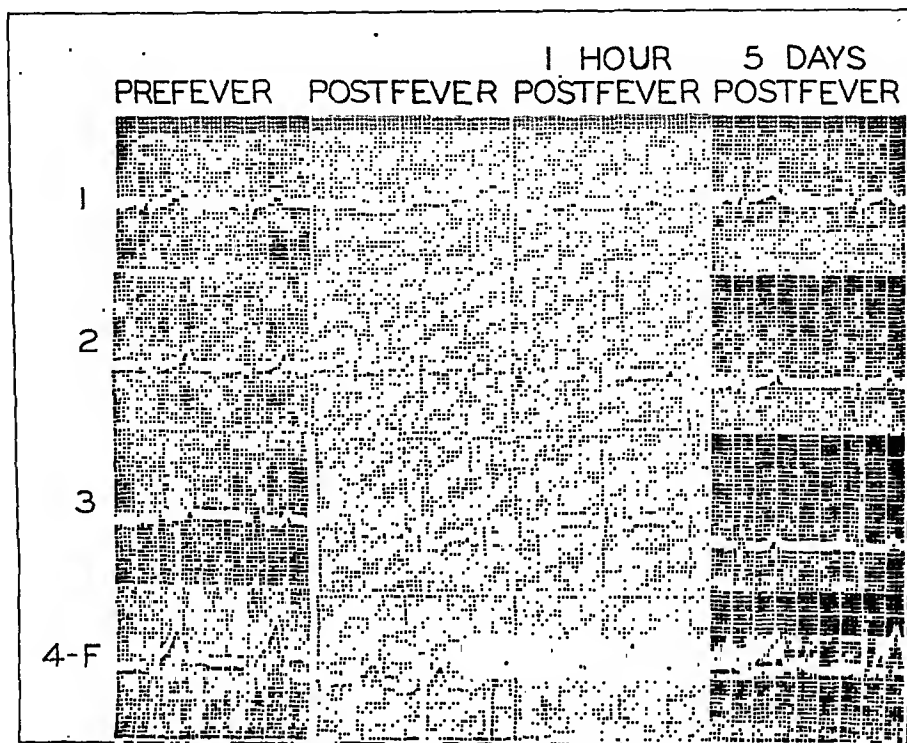


FIG. 3.—Electrocardiograms of Case 5881, showing definite change between the tracing taken immediately following fever and one taken 1 hour later. The CR leads were omitted from the illustration as they showed no change. A, Relationship of increase of rate to ECG changes. B, Relationship of fever to ECG changes. C, Correlation of amount of fever with the degree of change in rate.

Discussion. Cases 5177, 5956, and 5883 obviously had myocardial damage, probably on the basis of small coronary artery occlusions. While the possibility of myocardial infarction without coronary occlusion was considered, it was felt that such would not account for the relapse which occurred in 2 of the cases.

While Cases 5956 and 5883, prior to their relapse, show series of tracings comparable to those presented by some authors² as being due to tachycardia rather than myocardial damage, it is felt that the burden of proof rests with the person who claims that changes of this magnitude and duration are not due to myocardial damage.

Although 2 of the above cases (5177 and 5883) had definite rheumatic histories, their pre-fever examinations and cardiograms were normal. There is no evidence to show that the subsequent course was related to the rheumatic fever.

In the remaining cases, ECG changes were transient, there were no objective signs or subjective symptoms referable to the heart, and the laboratory work was entirely normal. Because of this, it is highly probable that the ECG changes were not on the basis of myocardial

damage, but rather were due to a temporary myocardial anoxia, possibly of a relative nature due to the tachycardia. Most cardiologists have seen inverted T waves following paroxysms of tachycardia. These inverted T waves, however, *rapidly* return to their normal upright position. It is probable that the cases in this group showing temporary changes fall into this category.

Cases 5880 and 6673 had tracings taken following exercise. Case 5880 showed no change but tachycardia, while Case 6673 showed depression of the S-T segments. The fact that the post-fever ECG changes were not reproduced in these patients, following exercise, does not rule out increased rate as a factor. The added factor of duration of the tachycardia undoubtedly plays a rôle. Were it possible to exercise a patient for the same length of time as that spent in the fever cabinet, changes similar to those found in post-fever tracings might be obtained.

Summary. 1. In a series of 118 electrocardiograms (ECG) taken immediately after fever therapy, the changes from the pre-fever tracings are tabulated. Of 80 tracings taken following therapeutic fever, 64 showed insignificant changes, 7 showed significant changes, and 9 showed no change whatever from the pre-fever tracing.

2. The results published by previous workers who claimed that the S-T segment was almost always depressed following fever are not confirmed. It was found that there was a slight increase or decrease in the amplitude of the P waves and the QRS complexes and that the S-T segment was depressed in a few cases. The most constant change observed was an increase in the value of Bazett's "K," an index of the duration of electrical systole.

3. The effects of jaundice, acid-base balance, and cardiac rate on the post-fever ECG are discussed.

4. Three cases with myocardial damage following fever therapy are presented.

5. Of these 3 cases, 2 apparently were almost completely recovered when each suffered a relapse, 39 and 56 days, respectively, following fever.

6. Six cases that showed transient and significant ECG changes, following fever, are presented. The possible causes of these changes are discussed.

Conclusions. While the majority of ECG changes following fever therapy are insignificant and probably due to the effect of tachycardia, it is possible to have changes due to severe myocardial damage, such as that caused by occlusion of a small coronary artery.

In those cases with myocardial damage due to fever, one should not give a good prognosis merely because the patient is young and the causative agent (fever) has been removed. The treatment of these cases should be the same as that given myocardial infarction due to any other cause.

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CONCENTRATED RED CELL TRANSFUSIONS

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IN recent years, with the establishment of many large blood banks, great quantities of plasma have been made and used, and as a by-product the settled erythrocytes were being discarded as a waste material. Generally, in the past, it has been little recognized that these concentrated red cells can be of definite therapeutic value, and in certain instances may even possess an advantage over the use of whole blood transfusions. More recently, however, interest in concentrated red cell preparations has become evident.

As early as 1918 Robertson¹⁰ described a technique for the administration of red cells to humans, and in 1937 Castellanos and Riera⁴ reported the successful use of red cells. In England there have been reports of the use of erythrocyte transfusions by McQuaide and Mol-lison (1940),⁸ Williams and Davie (1941),¹⁶ Vaughn (1941),¹¹ Whitby (1941),¹³ and Watson (1943).¹² In 1942 Bagdasarov² mentioned their use in Russia. More recently, in this country, Alt,¹ Evans,⁵ and Murray *et al.*⁹ have reported on successful series of transfusions of concentrated red cells.

The object of this report is to call attention to the use of concentrated red cell transfusions; to demonstrate that they are as efficacious as whole blood in raising the hemoglobin level; that no deleterious effects result from their administration; and in certain instances that they possess an advantage over whole blood.

Procedure. The concentrated red cell preparations were obtained from regular hospital donors. The Fenwal apparatus, a semi-closed system, was used to collect 500 cc. of blood in 50 cc. of 5% sodium citrate solution. The blood was typed by the open slide microscopic method and then stored at 4° to 6° C.

The red cells were usually prepared for use as the occasion arose for them, for it is our impression that the life of the cells is decreased when they remain in the concentrated state too long. Whenever obtainable, the blood of the patient's own group was used; otherwise group O blood was used. The blood selected was from 2 to 7 days old, in accordance with the findings and recommendations of Wiener and Schaefer¹⁴ and Belk and Barnes.³ Before preparation the donor's blood was cross-matched with that of the recipient by the test tube method of Landsteiner.¹⁵ If blood of more than one donor was to be

used in a transfusion, each donor blood was cross-matched with the recipient and also with the other donor bloods. Under sterile precautions the plasma was aspirated off into a pooling flask; the pipette was then inserted to the bottom of the bottle and the red cells aspirated into a different bottle, leaving the buffy coat or gel, which is composed of leukocytes, platelets and fibrin. All those cells to be used in the same transfusion were aspirated into the same bottle. The cells obtained from one donor blood in this way were called one donor unit of CRC. Following preparation, the CRC (concentrated red cells) were either used immediately or returned to the refrigerator until used. The CRC were never kept longer than 2 days after preparation.

The CRC were administered in regular Upjohn recipient sets which were equipped with metal screen filters. We did not find it necessary to dilute the CRC prepared in this manner in order to maintain the flow. We varied our regular transfusion procedure only by elevating the reservoir of blood approximately 3 feet higher than the usual level of 3 feet above the antecubital fossa to obtain a greater head of pressure. There was no difficulty in maintaining adequate flow by this method; 30 minutes was the average time required to administer each donor unit of CRC.

Composition of CRC. Listed below is a fairly typical example of the composition of one donor unit of CRC:

Volume	225 cc.
Hemoglobin*	21.9 gm./100 cc.
Hematocrit†	71.3%

* All hemoglobin determinations were performed by the Sahli method.

† All hematocrits were done in Wintrobe tubes.

We have divided our patients into several groups, according to the type of study that was carried out and the amount of cells given.

Group I: In this group only one unit of CRC was given at a time; blood pressure and temperature recordings were taken before the transfusion, the blood pressure after, and the temperature at 1, 2 and 4 hours after its completion. The patient's hemoglobin, hematocrit, non-protein nitrogen, and icterus index were determined before and 1 day after the transfusion; urinalyses were also done on the same days. On the 3rd and 7th days after the transfusion the patient's hemoglobin and hematocrit were again determined.

Group II: This consisted of adult patients who received more than one donor unit of CRC at a time, the children who received CRC in excess of one-half the amount calculated by allowing 10 cc. per pound of body weight, the amount recommended by Holt and McIntosh⁶ as being the maximum allowable without danger of overloading the circulation. The same procedure of study was used for this group as in Group I, except that after the 3rd day following the transfusion the hemoglobin and hematocrit were irregularly followed.

Group III: These are patients who received varying quantities of CRC at varying intervals and who were not followed as completely as the previous groups.

Results. Group I. Twenty-five transfusions of one donor unit of CRC each were administered to 19 patients. The average rise in hemoglobin the first day following transfusion was 1.22 gm., the 3rd day, 1.18 gm., and the 7th day, 0.86 gm. The hematocrit rise on the same days were, respectively, 3.8%, 3.4% and 2.4%. In a few indi-

vidual cases the non-protein nitrogen rose slightly, but in the whole group averaged a slight decrease. The icterus index rose in a few cases, but generally the increase was slight and insignificant (Table 1). In all patients the urine showed no significant change.

Group II. Twenty transfusions were given to 14 patients. The average increase in hemoglobin on the 1st and 3rd days following the transfusion were respectively, 2.22 gm. per transfusion or 1.05 gm. per donor unit, and 2.04 gm. per transfusion or 0.93 gm. per donor unit. On the same days the average hematocrit rise was 5.5% per transfusion or 2.6% per donor unit, and 5.1% per transfusion or 2.3% per donor unit. The changes in the non-protein nitrogen and the icterus index were approximately the same as in Group I, except for one case in which the icterus index rose considerably following a transfusion reaction (Table 2).

Group III. Seventy-nine transfusions were given to 17 patients (2 of these patients were also in Group II). Among these the results compared favorably with those of Groups I and II. It was impossible to follow many of the patients accurately, since CRC and whole blood were irregularly and intermittently given; also some of the patients receiving the transfusions showed signs of active blood destruction or blood loss. However, from intermittent blood studies as well as clinical observation, it was our impression that transfusions of CRC were as beneficial as whole blood. In Table 3 are listed a number of patients who were anemic, were not bleeding, and who demonstrated no signs of active blood destruction at the time of receiving the CRC transfusions. In these patients the average rise of hemoglobin per donor unit of CRC given was 1.5 gm./100 cc., an increase slightly higher than those of Groups I and II; this would be expected by the type of anemia of the selected patients listed in this table.

Following are the case records of a few typical patients elected to receive CRC:

CASE 1. A 40 year old white male was admitted 8/26/43 to the Medical College of Virginia Hospital with a chief complaint of vomiting and spitting blood, of 2 days' duration. The laboratory studies showed the hemoglobin was 13.6 gm.; the R.B.C. were 4,810,000; W.B.C. were 7650. A Roentgen ray of the throat revealed a soft tissue mass in the region of the larynx. A laryngoscopy was performed and a biopsy of the mass showed a Grade I carcinoma of the larynx. On 9/6/43 the patient received the first of a series of Roentgen ray treatments, and that night he began to hemorrhage from his throat. This continued intermittently for 6 days, and during that time he received multiple whole blood transfusions to maintain his hemoglobin level. On 9/12/43 the bleeding ceased. At this time the hemoglobin was 3.7 gm. and transfusions of CRC were started. In 7 days seven donor units of CRC were given and the hemoglobin rose to 14.9 gm. The Roentgen ray treatment was resumed on 9/10/43 and a total of 2500 R units were given. On 9/21/43 the patient was discharged for ambulatory treatment.

This represents a case of post-hemorrhagic anemia treated with CRC. The patient received an equivalent of 7 whole blood transfusions in 4 transfusion procedures, in 7 days as CRC. The CRC transfusions were not used to maintain the blood volume or combat shock; whole blood was used for this. The CRC transfusions were started and continued until the blood volume and plasma proteins were normal.

TABLE 1.—PATIENTS OF GROUP I

Patient	Hemat. of CRC*	Age of CRC* (days)	Gm. Hgb. % Hemat. } of patient at intervals				Hgb. rise after 7 days	NPN		Icterus index		Reactions Sl. chill, temp rise of 3°
			Before transf.	1 day after	3 days after	7 days after		Before	After	Before	After	
C M 17 Boeck's saroid	71.0	3	11.0 40.0	12.3 44.0	12.2 40.0	11.5 42.0	0.5 2.0	33	49	4	14	
C M 40 Pemphigus	64.0	6	7.7 30.0	8.6 31.5	8.2 30.5	7.8 30.5	0.1 0.5	24	?	5	6	None
C M 61 Chronic nephritis	70.0	4	5.9 27.0	7.2 29.5	7.5 ?	7.3 29.0	1.4 2.0	144	124	7	6	None
C F 17 Gen. arthritis	64.0	4	12.0 41.0	13.5 45.0	14.0 45.0	13.0 46.0	1.0 5.0	24	27	4	8	None
C M 61 Chronic nephritis	71.5	5	6.0 26.0	7.2 31.5	6.2 30.0	102	86	4	5	None
C M 42 Lung abscess	71.0	4	7.0 32.0	8.4 37.0	9.8 36.0	8.4 34.0	1.4 2.0	26	31	5	7	None
C M 22 Diabetes mellitus	76.5	4	5.5 23.0	6.5 26.0	6.3 25.0	5.2 21.5	-0.3 -1.5	34	34	5	5	None
C F 16 Postoperative anemia	73.0	4	7.8 30.0	10.8 39.5	8.7 35.0	8.4 33.0	0.6 3.0	25	26	4	5	None
C F 34 Postoperative anemia	76.0	5	10.8 41.0	11.6 41.0	11.2 40.5	11.0 40.0	0.2 -1.0	28	29	5	5	None
C F 40 Posthemorrhage anemia	71.0	5	6.4 29.0	7.7 33.5	8.5 39.0	8.4 39.0	2.0 10.0	30	28	8	20	None
C M 52 Rheumatoid arthritis	76.0	6	7.5 32.5	8.5 32.0	8.2 32.0	7.8 32.5	0.3 0	27	27	8	10	None
C F 40 Posthemorrhage anemia	75.0	5	6.3 30.0	7.7 34.0	8.2 36.5	7.8 34.5	1.5 4.5	27	24	3	7	None

C M 52	84.0	6	7.4	8.0	8.2	8.0	0.6	26	31	8	12	None
Rheumatoid arthritis			32.5	33.0	33.0	31.5	-1.0					
C M 52	75.0	5	6.4	7.0	8.3	8.2	1.8	52	50	12	15	None
Duodenal ulcer			32.0	34.0	35.0	36.0						
C F 47	71.0	3	9.5	10.4	10.8	10.0	0.5	28	33	5	8	None
Cancer of rectum			35.0	38.0	39.5	39.5						
C M 33	72.0	3	10.9	12.7	12.5	12.3	1.4	30	32	5	7	None
Paresis			43.5	47.5	47.0	46.0						
W M 60	73.5	4	12.5	13.9	13.0	38	42	15	15	None
Lymphatic leukemia			44.5	47.0	45.5							
C F 17	77.5	3	5.3	6.9	6.5	6.1	0.8	42	29	6	9	None
Gc. arthritis			20.5	27.5	25.0	24.0	3.5					
C F 18	69.0	4	5.4	7.0	7.3	7.4	2.0	27	25	45	50	None
Sickle cell anemia			20.0	28.5	27.0	28.5	8.5					
C M 52	65.0	2	7.8	8.5	8.3	8.1	0.3	29	27	10	10	None
Rheumatoid arthritis			31.0	35.0	33.5	34.0	3.0					
C M 49	76.0	2	6.8	7.8	7.3	7.6	0.8	78	71	8	8	None
Luetic heart disease			26.0	30.0	28.5	26.5	0.5					
C F 18	70.0	2	7.4	8.5	8.5	8.0	0.6	31	29	50	50	None
Sickle cell anemia			28.5	32.0	31.5	29.5	1.0					
C M 44	85.0	..	7.3	9.0	8.7	4	4	None
Pleurisy with effusion			34.0	38.0	38.0							
W M 31	57.0	4	10.0	11.3	11.0	10.5	0.5	28	27	20	20	None
Typhoid fever			37.0	40.0	..	34.5	-2.5					
W M 45	71.0	4	10.2	11.1	11.6	11.2	1.0	34	37	7	8	None
Melanosarcoma			34.0	41.5	41.5	38.0	4.0					

* CRC = Concentrated red corpuscles.

TABLE 2.—CHART PRESENTING PATIENTS OF GROUP II

Patient	Hgb. Hemat. of donor CRC*	Amount given (cc.)	Gm. Hgb. % of patient at intervals						NPN		Icterus index		Reactions and remarks	
			Before transf.	1 day after	3 days after	5 days after	10 days after	Before 42	After 42	Before 25	After 25			
W M 52 Lymphatic leukemia	21.8 71.0	540	6.5 21.5	8.5 26.0	8.2 25.0	44	48	15	?	No clinical jaundice
"	23.0 72.0	600	8.2 25.0	8.7 26.0	8.1 24.5	44	..	25	25	None
"	21.5 69.0	600	8.1 24.5	9.8 25.0	44	..	25	25	None
C F 42 "Chronic anemia"	23.0 74.0	700	3.5 18.0	6.2 26.0	4.3 19.5	..	6.7 28.0	26	30	15	15	Clin. icteric 2 days after, soon cleared
C M 4 Nutritional anemia	20.2 70.0	200	10.4 43.0	12.5 48.0	12.0 48.0	11.0 44.0	36	40	15	15	None
W F 12 Rocky Mt. spotted fever	21.0 70.0	200	11.1 36.0	11.0 34.0	28	..	10	15	Chill, temp. rise of 2.8°
W M 9 mos. Celiac disease	18.5 68.0	125	8.5 37.0	10.7 43.0	10.8 43.0	8	10	None
"	18.5 68.0	110	10.8 43.0	13.0 46.0	13.5 45.0	8	12	None
W F 21 Rocky Mt. spotted fever	24.2 74.0	500	10.4 34.0	12.0 42.0	13.6 44.0	26	35	8	12	None
C M 5 Sickle cell anemia	18.6 61.0	250	5.9 23.0	8.6 28.5	37	50	50	None

	"	"	"	20 8 70.5	250	8.6 28.5	11 0 33.5	50	50	None
W F 21				22 6	500	13.6 44.0	15.0 48.5	14.7 48.5	35	42	15	None
Rocky Mt. spotted fever				72 0										
C F 3				..	250	7.5 29.0	11.5 42.0	11.0 39.0	27	28	20	None
Sicklo cell anemia				64.0										
W F 20				22.0 72.0	450	5.8 23.0	8.1 27.0	37	36	10	None
Leukemia														
C F 55				23.5 73.0	450	8.4 30.0	10.5 31.5	..	10.2 35.0	..	34	34	5	None
Hyperthyroidism														
C M 58				22.5 70.0	600	9.2 33.0	12.5 41.0	12.6 41.0	33	39	5	None
Lung abscess														
C F 23				22.9 71.0	525	6.6 28.5	10.1 32.0	..	4.3 18.5	..	48	54	8	Very ill before transfusion
Lupus erythematosus														
C F 49				24.0 76.0	500	8.0 29.5	9.3 29.5	36	?	7	None
Postoperative anemia														
C M 14				21.2 69.0	450	11.2 28.0	13.1 40.0	30	28	5	None
Postoperative anemia														
C F 23				22.8 73.0	450	4.3 18.5	6.5 25.5	54	50	8	Very ill before transfusion
Lupus erythematosus														
Av. rise Hgb. 1st day { 2.22 per transfusion 1.05 per donor unit														
Av. rise hemat. 1st day { 5.5 per transfusion 2.6 per donor unit.														
Av. rise Hgb. 3rd day { 2.04 per transfusion 0.93 per donor unit														
Av. rise hemat. 3rd day { 5.1 per transfusion 2.3 per donor unit														

* CRC = Concentrated red corpuscles.

TABLE 3.—PATIENTS OF GROUP III, SELECTED FROM THOSE WHO SHOWED NEITHER ACTIVE BLOOD LOSS NOR BLOOD DESTRUCTION

Diagnosis	No. of CRC units given*	Total rise of Hgb. in gm.	Av. rise of Hgb. per CRC unit
Carcinoma of larynx—acute blood loss	7	11.2	1.6
Chronic blood loss	6	9.9	1.6
Chronic nephritis	1	1.2	1.2
Leukemia	4	4.8	1.2
Gas gangrene	3	5.1	1.7
Carcinoma of rectum	6	5.2	0.9
Splenic anemia	2½	2.7	1.1
Subphrenic abscess	1	2.4	2.4
Acute blood loss	3	4.0	1.3
Anemia ? ?	2	4.8	2.4
Average rise of Hgb. per unit CRC			1.5

* In several cases 2 units of CRC were given in 1 transfusion.

CASE 2. This 12 year old colored child was admitted 8/4/43 with sickle cell anemia. He had multiple ulcers of both legs, frequent bouts of abdominal cramps, and occasional joint pains. He had been admitted to the hospital in November of 1942 and after receiving multiple whole blood transfusions was discharged very much improved. His blood gradually declined until the present admission, at which time the R.B.C. were 1,870,000 and the hemoglobin was 6.8 gm. The patient was given 3 donor units of CRC and the hemoglobin rose to 10.2 gm.; however, following this, sickle cell crisis supervened as evidenced by acute joint and abdominal pain and severe jaundice. This continued for 3 weeks, during which period the hemoglobin was maintained at about 8 gm. by the administration of 4 donor units of CRC. When the symptoms abated the hemoglobin was 8.2 gm. Three more donor units of CRC were given and the hemoglobin rose to 11.6 gm. On 9/29/43 the patient was discharged with the leg ulcers healed and very much improved symptomatically.

The above is a good illustration of the use of CRC in the maintenance of the hemoglobin during a bout of acute blood destruction. In this case there was no need for replacement of blood volume or of proteins, the only element of the blood required being the red cells. By using CRC in this case (a total of 10 donor units) approximately 2½ liters of plasma that would have been given with the whole blood were saved for more essential use.

CASE 3. This 65 year old white female was first admitted to the Medical College Hospital on 2/2/42 with the complaint of weakness, anorexia, lassitude, and weight loss which had become progressively worse for the previous 8 months. Laboratory studies: R.B.C. 1,200,000, hemoglobin 3.7 gm., W.B.C. 4500. Complete hospital studies lead to no diagnosis other than anemia of unknown etiology. The patient received a series of transfusions and was discharged very much improved symptomatically; however, she was admitted on 5 other occasions during the year, each time receiving multiple transfusions with relief of symptoms. She died 2 days after the final admission on 1/17/43 with pneumococcic meningitis. Her hemoglobin level was maintained for approximately a year with 18 whole blood transfusions and 17 CRC transfusions of one donor unit each. Of the 18 whole blood transfusions, 15 were followed by febrile reactions of a moderate to severe nature. Every available method to discover the incompatibility of the patient's blood was used without success. Of the 17 CRC transfusions only 3 were followed by reactions, and these were relatively mild in nature. Whenever AB blood was available it was used as whole blood; however, frequently this was not possible and Group O CRC were used at these times.

This woman represents a case of anemia of obscure etiology treated by multiple transfusions. It illustrates well the low reaction rate of CRC and the desirability of their use in the rare patient who reacts to whole blood transfusions consistently, with no evidence of incompatibility discoverable; it also illustrates the relatively small danger of using O cells when the blood of a patient's specific group is not available.

CASE 4. A 28 year old housewife was admitted 9/4/43 with a chief complaint of vaginal bleeding and swelling of the face and extremities. There was a severe hypochromic anemia with a hemoglobin of 4.2 gm. On 9/7/43 a dilatation and curettage was done and the bleeding ceased within a few days. The patient received several whole blood transfusions with a moderate rise of hemoglobin level. On 9/10/43 the patient first developed signs of uremia and complete studies revealed renal insufficiency with hydronephrosis and ptosis of the right kidney. The patient then developed congestive failure, and on 9/12/43 her non-protein nitrogen was 124 and the hemoglobin level was 5.4 gm. Because of the congestive failure it was decided that she should receive CRC; in 3 days she received 3 donor units of CRC and her hemoglobin rose to 9.4 gm. With further supportive treatment the uremia subsided, and later other procedures were carried out to correct the ptosis and hydronephrosis of the right kidney.

This represents a case in which there was a need for hemoglobin; however, because of the uremia and congestive failure, there was a danger of overloading the circulation and producing pulmonary edema by large amounts of parental fluids. Transfusions of CRC were advantageous here, furnishing the same amount of hemoglobin present in whole blood in half the volume of fluid. Following the administration of 3 donor units of CRC the hemoglobin rose from 5.4 to 9.4 gm., and with other supportive treatment the uremia subsided.

Reactions. Of the series of 124 transfusions there were 11 reactions, or a total of 8.9%. Nine reactions consisted of chills and fever, 1 was allergic in nature (urticaria), and 1 was a hemolytic reaction 2 days following a transfusion. Of these 11 transfusion reactions, 5 occurred in 20 transfusions given to 2 patients who received CRC primarily because they reacted to the majority of whole blood transfusions, despite all attempts to find a source of incompatibility (Case 3 was one of these patients). Discounting these 2 patients, there were 6 reactions among 104 transfusions, or a total reaction rate of 5.8%. In the first 3000 whole blood transfusions given through our blood bank, the total reaction rate was 7.8%.⁷ From these data it may be concluded that the reaction rate with the use of CRC in the average patient requiring blood is lower than with whole blood. We have also observed that the reactions which do occur are usually milder than those which occur with the use of whole blood. An opportunity presented itself to observe this difference in the 2 patients mentioned above; the chills were not as severe or as prolonged and the temperature elevation was less marked.

Discussion. In our series of 124 CRC transfusions we have found that CRC are as efficacious as whole blood in raising the hemoglobin of anemic patients; and in certain instances they possessed an advantage over the use of whole blood. With the use of CRC more

hemoglobin can be supplied an individual in the same volume of transfused fluids; this reduces the number of procedures and the time necessary to raise the hemoglobin to a given level. However, it was our impression that the hemoglobin rise per donor unit of CRC used was greater when single donor unit transfusions were given over a period of time rather than multiple donor unit transfusions in one procedure. Conversely, the same amount of hemoglobin can be supplied in a smaller volume of transfused fluid. It follows then that CRC could be of definite value in relieving the anemia of patients with a reduced cardiac reserve, by reducing the chances of the production of cardiac failure and pulmonary edema. Theoretically it would also be of value to use CRC in patients who have recently hemorrhaged and in whom there is danger of dislodging a newly formed clot by increasing too greatly the volume of circulating fluid with quantities of whole blood (*e. g.*, bleeding peptic ulcer).

In practically every previous report there has been described a reduced number of reactions with the use of CRC transfusions. This is presumably because the greater portion of the plasma has been removed. We too have found this to be true and have used CRC to advantage in patients who experience reactions to most transfusions of whole blood. It is also well to remember that Group O CRC may be given to patients of a different blood group with less danger of a reaction than with the use of universal whole blood.

Many patients receive whole blood transfusions when only the cellular elements of the blood are needed. If CRC were used for the many cases in which they are indicated, an additional quantity of plasma would be available for other important uses. It has been estimated in the Medical College of Virginia Hospital that about one-half of the transfusions given are to raise the hemoglobin level only. Last year about 3000 transfusions were given; thus, approximately 1500 could have been converted to plasma and red cell concentrates, thereby saving 185 liters of plasma.

It must be realized that CRC transfusions have their limitations. They should not be used in cases of acute blood loss until the blood volume has returned to normal, and the only deficit is in hemoglobin. Their use is contraindicated in shock, burns, and when the plasma proteins are below normal. The uses of CRC are not limited merely to elevating the hemoglobin level; Evans⁵ has reported that CRC were apparently as efficacious as whole blood in controlling the bleeding and other purpuric manifestations of the blood dyscrasias. We have observed the same beneficial results in a 12 year old female diagnosed as having monocytic leukemia.

Summary. 1. A procedure for the preparation of CRC is described.

2. It is shown that CRC transfusions are as efficacious as whole blood in raising the hemoglobin of anemic patients in whom only the cellular elements of the blood are deficient.

3. The reaction rate with the use of CRC in the average patient is 5.8% and is 8.9% in the entire series of transfusions to all patients.

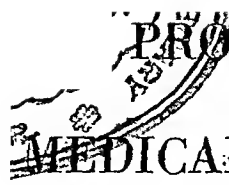
4. Certain advantages of the use of CRC transfusions over whole blood are presented and 4 case histories are reviewed as illustrations.

5. The indications for and the contraindications to CRC transfusions are discussed.

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PROGRESS OF MEDICAL SCIENCE

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THE SYSTOLIC MURMUR

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NEW ORLEANS, LA.

THE introduction of auscultation of the heart led quickly to the recognition of sounds other than the usual heart tones and an association of those sounds with cardiac damage. It was in 1809 that Allen Burns, a lecturer on Botany in Glasgow, described unusual sounds produced by the heart in a case where the mitral valve was indurated and the pericardium inflamed.²⁵ He described a hissing noise. Since that time the pendulum of opinion on the interpretation of murmurs has swung from one side to the other. Interest in the significance of these murmurs has been greatest in times of war when the question of physical fitness has reached the importance it routinely deserves.³³

Levine points out that, when it is realized that patients have compensated organic valvular disease for many more years than they have heart failure and that they often desire to know whether heart disease of any sort exists, the importance of this subject is appreciated.^{24b} The great interest in recent years in the efficiency of heart muscle as an index of the extent of damage in the heart has had some effect in minimizing the importance of murmurs. It is sometimes stated that the efficiency of the heart muscle often has greater significance than murmurs in the diagnosis of cardiac disease.³⁸ This is at times true; but there are also numerous occasions on which the murmur carries greater weight in the diagnosis than does the condition of heart muscle.

Whereas the diastolic murmur has received the greatest respect in cardiac diagnosis, the systolic murmur is known to occur frequently without an anatomic cause. Laennec knew that the murmur was often heard in the absence of heart disease, and we, a century and a quarter later, still frequently find ourselves unable to determine when such a murmur indicates, and when it does not indicate cardiac valvular damage. The early interpretation of cardiac murmurs did not take into consideration transmission of the murmur, history of rheumatic fever, or enlargement of the heart. The differential diagnosis of physiologic and pathologic murmurs was not well established and cardiac murmurs were synonymous with valvular defects. For many years, even though it was recognized that some mur-

murs occurred in the absence of valvular defects, as shown by postmortem examination, the fact that murmurs were sometimes associated with heart disease led to a frequent assumption that a heart with murmurs was a diseased heart. In the period about 40 to 50 years ago the pendulum swung to the other extreme and the teaching became worldwide that systolic murmurs had no significance. It is obvious at present that neither of these extreme views is the correct one and that the truth lies somewhere in between. Confusion in the interpretation of systolic murmurs at the time of the first World War is evident from the fact that at first men with such murmurs were turned down for military service. Through the advice of Lewis, the regulations were later changed so that those with systolic murmurs, in the absence of other evidences of heart disease or a history of rheumatic fever, were accepted.

Frequency. The importance of the problem is reflected in Reid and Pharr's statement that systolic murmurs were found in 20 to 35 % of normal youthful patients.³⁷ Blumenthal⁷ found approximately 23 % of the patients attending cardiac clinics were normal, and that 25 % of these normal individuals had systolic murmurs. Others have estimated the occurrence of systolic murmurs in children at 40 to 70 %, and in older age groups at from 20 to 35 %.¹³

Rauh³⁵ found in 710 children from the first to the eighth grade in a school survey in Cincinnati, that 20 % had such murmurs. In 5541 high-school students from 12 to 19 years of age, Schwartzman³⁹ found 134 (2.42 %) with organic heart disease, and 43.9 % with physiologic murmurs. The latter is a seemingly high figure, which was greatly increased by exercise to 83.6 % of those without a murmur at rest. Some believe that especially in children²⁹ a large percentage of soft murmurs is significant.

Contratto¹⁰ in 2856 college students found systolic murmurs in 350 (12.3 %), 7.3 % of which were classified as "functional." In 127 (4.6 %) the intensity and location precluded a functional classification and there were not sufficient findings to diagnose heart disease. These figures show the importance of the detection, interpretation and evaluation of murmurs as signs of heart disease.

Classification. It has been traditional to term murmurs *organic* when caused by valvular damage, abnormal orifices and constrictions produced by pathologic disturbances in the vascular system. The terms *functional*, *accidental*, *hemic*, *accessory*, *adventitious*, *atonic*, *non-pathologic* and *non-organic* have been applied to the others. Some have classified murmurs by a dichotomous system,¹¹ first, those occurring in normal individuals, and, second, those found in individuals with disease. In normal persons, murmurs have been further classified into temporary and permanent. In patients with disease, they have been separated into those caused by cardiac disturbances, such as endocardial, valvular, myocardial and congenital disease, and those resulting from generalized disease, such as anemia, hypertension, infection and fever. This system can be simplified by classification of murmurs into 4 groups—those occurring in the absence of disease, those occurring in generalized disease, those resulting from endocardial and from myocardial damage.

White, Adams and Craib⁴⁷ have found the terminology in general use unsatisfactory and confusing, a point of view with which the writer heartily agrees. The use of the term *functional*, for example, describes murmurs found in 2 entirely different types of patients—normal individuals and those with a dilated valvular ring or heart chamber from cardiac or extracardiac disease. Such a term, therefore, covers murmurs of no

importance and murmurs resulting from serious myocardial damage. They propose the following classification:

I. Physiologic murmurs.

A. Intracardiac or intravascular.

B. Extracardiac.

(a) Cardiopulmonary.

(b) Pericardial.

II. Pathologic murmurs.

A. Due to structural valvular disease.

B. Due to congenital cardiovascular defects.

C. Due to dilatation of ventricles, aorta, or pulmonary artery from: (a) cardiovascular disease; (b) other diseases, such as anemia, thyrotoxicosis, severe infection.

D. Due to pericarditis.

According to this terminology, as further described by White, Adams and Craib, physiologic murmurs are frequently found in normal persons. The intracardiac and intravascular varieties are almost always systolic and occur chiefly over the pulmonic and apical areas. Such murmurs are usually soft and blowing, high pitched, short, often beginning late in the cardiac cycle and ending before the second sound, and are rarely holosystolic. They are heard over a limited area, but at times may be transmitted. Frequently they are inconstant, appear after exercise and vary with the position of the body. They are usually loudest when the patient is lying down and at the end of, or during, inspiration, although they may be heard at the end of expiration. Approximately 50% are heard in both inspiration and expiration. Deep breathing may exaggerate them. They do not replace the first sound.

The cardiopulmonary murmurs of the extraeardiac variety result from the action of the heart upon aëration in the lung. They are usually systolic, blowing and relatively faint, but may be transmitted into the axilla. They are at times difficult to differentiate from intravascular murmurs, but if the patient stops breathing at inspiration or full expiration, or even at any point in the respiratory cycle, they usually cease. Sometimes, however, they may continue. Extracardiac murmurs over the heart may be intravascular. Examples of this are the venous hums in the neck which are sometimes heard in the upper chest, and the venous hum transmitted from the epigastrium, occurring at times in the Cruveilhier-Baumgarten syndrome. Occasionally unusual situations occur, such as that described by Maliner,²⁸ in which a cavernous hemangioma in the left epigastrium produced the murmur. Pericardial sounds are scratching, systolic, diastolic or both, heard just along the left border of the sternum, especially after exercise or in thyrotoxicosis. Explanations for their presence include compression of the pericardial surfaces by the vigorously acting heart.⁴⁷

Pathologic murmurs, as described in the classification of White, Adams and Craib, include some murmurs commonly called functional because they occur with normal valves in cardiac dilatation. It may be difficult or impossible to determine whether or not pathologic murmurs result from deformed valves. Those due to pericarditis are the well-known friction rubs, not usually considered under the term, *murmur*. They are systolic, or systolic and diastolic, in time, scratchy in character, best heard near the left border of the sternum or between the sternum and apex. They will not be discussed here.

The above terminology will be adhered to in the remainder of this

discussion, which is concerned primarily with the problem of differentiation of the physiologic murmur from pathologic murmurs representing cardiovascular disease. This phase of the problem is most important for it is a greater error to make the diagnosis of organic heart disease in a person with a normal heart than it is to make a diagnosis of a normal heart in an individual with a minimal lesion, without any other cardiac findings.¹⁰

No discussion will be given concerning the factors underlying the development of murmurs. It is well known that when the circulation speeds up to a point where turbulence in flow occurs, murmurs are likely to develop. Since the greatest velocity occurs in systole, the greatest number of murmurs is likely to develop in that time. This point is often reached in exercise, febrile states, hyperthyroidism and conditions causing reduced blood viscosity, such as anemia. Turbulence of flow also results from valvular damage, such as insufficiency or stenosis with constriction of arteries, and from abnormal openings, as in congenital heart disease.

Characteristics of Systolic Murmurs. *Thrills.* Attempts to differentiate physiologic murmurs from the pathologic variety have brought to light many characteristics—some time-honored—which are useful in such differentiation. Most of these characteristics are periodically subject to review^{9,22,25} and will be but mentioned here. The presence of a thrill, the palpable counterpart of the murmur, usually brands the murmur as significant. A thrill is not something apart from the murmur, but indicates merely that of the vibrations produced by the turbulent flow, there are enough of sufficient intensity and proper wave length to produce palpable sensations. Intensity, therefore, enters into this concept. All murmurs with accompanying thrills (all thrills, therefore) do not signify organic heart disease. Such vibrations are felt at times in hyperactive hearts, as in hyperthyroidism, or with certain systolic murmurs, especially in the pulmonic area, in the absence of organic heart disease. However, the prolonged purring sensation which is definitely the counterpart of a murmur almost invariably brands that murmur as pathologic.

Quality. Quality and high or low pitch of murmurs, blowing quality, harshness, whistling and musical character⁸ are factors of importance in the interpretation of systolic murmurs. It has been suggested that sound records might be helpful in the differentiation of physiologic and pathologic murmurs. McKee³² points out that the apical systolic murmurs present in cases of mild cardiac damage appear similar to those found in normal records except for increased intensity. She points out, too, that with more advanced heart disease these murmurs become slightly higher in pitch. Manheimer³⁰ felt that, with filtration of frequency ranges, differentiation could be made between organic and physiologic murmurs and that the method should complement auscultation. Bartlett and Carter⁴ profess to differentiate by stethograms systolic murmurs which are significant from those which are not. Criteria are given for this differentiation, but proof of the state of the patient's heart by autopsy is the only safe criterion to check such records and this apparently was not done. Certainly others,^{20,48} including the writer, are not convinced of the superiority of sound tracings over the human ear, especially for pitch and loudness, although systolic murmurs may be seen in records when not heard.¹⁹

At times sound tracings may be helpful by the addition of supportive evidence for a systolic murmur. The diastolic rumble is at times difficult to hear and may be recorded when not audible or when the murmur is

little more than a prolongation of the third heart sound. Likewise events in diastole, split sounds and gallops, may be recognized as heart tones and differentiated from murmurs by the sound tracings.^{21,45}

Transmission. Transmission of the murmur adds weight to its interpretation as pathologic. Apical murmurs transmitted into the left axilla and back fall into this group. In some instances transmission is extreme and the murmur may be heard completely around the chest. This phenomenon is described as Couto's circular murmur.^{3,34} Further remarks on transmission are included under *Intensity*.

Duration. Two other characteristics of systolic murmurs are of great value in their interpretation. Duration of the murmur is one. A murmur, especially an apical murmur, which persists throughout systole, holosystolic therefore, is usually pathologic. This is particularly true if it replaces the first heart tone.

Confirmatory Reliable Signs of Heart Disease. Finally, and of greatest importance is the presence of other findings diagnostic of heart disease. Cardiac enlargement, a diastolic murmur, alternating pulse, for example, would indicate definite organic heart disease and the accompanying systolic murmur would be considered pathologic.

Intensity. It will be noted that the first 3 characteristics described above were definitely related to intensity of the murmur. The louder the murmur the more likely the transmission. Transmission, especially of apical murmurs to the axilla or back, gives a greater significance to the murmur than if it is localized. Intensity also enters into the obliteration of the first sound when the murmur is instituted with the beginning of systole.

The factor of intensity has received much attention in the interpretation of murmurs. It is not an index of the degree of heart disease, for a slight leakage with vigorous ventricular contraction may give a loud murmur, whereas ventricular dilatation may cause the murmur of great leakage to fade. At times, loud murmurs, even with a thrill, may be heard and yet normal heart valves are found at autopsy.¹³ Such circumstances are unusual.

Both Levine^{24a} and White⁴⁶ give great weight to the intensity of the murmur. Levine feels that all loud murmurs indicate heart disease. He states that we specify the amount and degree of albuminuria and glycosuria in quantitative terms and that the application of the quantitative methods of murmur intensity is also most helpful in diagnosis. He grades murmurs in 6 classes. Grade 1 describes the faintest murmur heard on careful auscultation, which has definite duration into systole to rule out prolongation of the first tone. Grade 6 is the loudest murmur, one which may be heard with the naked ear at some distance from the chest. Grades 2 through 5 are intermediate and are called slight, moderate, loud and very loud. He finds that nearly all murmurs in Grades 3 and 4, or greater, are associated with organic heart disease. In 1000 patients chosen at random from various hospital services, he found that 19.6% had murmurs of Grades 1 and 2. If those with a history of rheumatic fever or with hypertension, anemia, neurocirculatory asthenia, hyperthyroidism and fever were taken out, only 45 (4.5%) remained; and in 34 of these the murmur was Grade 1. He found that in normal individuals, exercise did not produce murmurs above Grades 1 or 2 in 10 subjects tested. Results of this study indicated that if systolic murmurs of Grade 2 or more were found with no conditions such as anemia, hyperthyroidism and the other factors mentioned above, to account for them, they probably were due to some organic change in the heart.

In 1927, White,⁴⁸ upon the basis of intensity, analyzed 1000 patients with apical systolic murmurs, divided into slight, moderate and marked groups. The slight ones constituted 490 of the 1000. Of these, 176 had apparently normal hearts and 276 (56%) had disease. It must be remembered that these patients were chosen from those sent to a cardiologist for evaluation and not at random from the general population. Many of the patients had other evidences of disease such as other murmurs or enlargement of the heart. Moderately loud murmurs constituted 240 of this group. Only 12 were thought to have normal hearts and of the 12, 6 were accounted for on an extracardiac basis. In the very loud group, which included 270 cases, there were only 2 normal hearts, 1 in a patient with anemia. White felt that the louder the murmur, the worse was the prognosis.

Baker, Sprague and White² have more recently followed up 187 patients who were seen 10 to 21 years previously with loud or very loud systolic aortic or mitral murmurs, corresponding to Grades 4, 5 and 6 of Levine. Diastolic murmurs were not present. Of these, 155 (82.5%) were dead, and in 122 (78.7%) death had been due to heart disease. In 74 (47.7%) death occurred within 1 year after the first examination; in 110 (70.8%) within 3 years. Only 24 of the 155 deaths occurred under the age of 50. In 24% of the deaths among those with rheumatic heart disease, subacute bacterial endocarditis was the cause. They found that systolic murmurs of this intensity are almost always associated with cardiovascular disease.

Baker, Sprague and White also state that such factors as pregnancy, anemia, hyperthyroidism and neurocirculatory asthenia probably do not produce loud murmurs. Friedlander and Brown¹⁶ carried out several procedures on a number of normal individuals to note the development and intensity of murmurs. In 100 patients with no heart disease, the administration of amyl nitrite to the point of full pharmacologic effect produced murmurs in 47, varying in age from 12 to 57 years. Most of the murmurs were heard at the base and none was louder than Grade 2. In only 4 of 26 patients with fever, produced by typhoid or malaria, did transient systolic murmurs appear, and none was as loud as Grade 3. These data constitute strong evidence in favor of the association of loud murmurs with organic cardiovascular lesions.

The effect of exercise on the appearance of murmurs is not constant. Norris and Landis¹⁶ found that 7.8% of 1552 students developed murmurs after exercise. Mackenzie's figure is 2.8% of 266 apparently healthy students. Siensen's figure^{41a} is 46% in 275 children and adolescents. Schwartzman's high figure³⁹ of 83% in school children after exercise has already been given.

Location. The location of the systolic murmur is of importance in its interpretation. In the *pulmonic area*, murmurs usually described as functional, that is physiologic, are heard in 60% of children under the age of 14 and are common in thin-chested individuals.²⁵ These are probably the commonest of all heart murmurs, are usually soft, occasionally rough, frequently loudest with the patient recumbent, and often are absent at some phase of respiration. They are frequently heard best at the end of deep expiration. Usually they are localized and do not replace the first sound. Exercise may bring them out. In this location, such murmurs usually occur without a background of organic disease and are variously ascribed to constriction of the pulmonary artery, dilatation of the artery, or its nearness to the chest wall. At times they may be associated with extracardiac lesions, such as pleural effusion or mediastinal glands,

which cause displacement or pressure. Pulmonary systolic murmurs due to heart disease may result from right ventricular enlargement, associated with pulmonary disease, mitral stenosis, patent ductus arteriosus or pulmonic stenosis. Because the pulmonic systolic murmur is so frequently found with the normal heart, other evidences, such as cardiac enlargement, diastolic murmurs, thrills or other reliable signs of heart disease, are essential to a cardiac diagnosis. Fortunately, it appears that when the murmur is significant, such corroborative evidence usually is present.

Murmurs in the *aortic area*, unlike those in the pulmonic area, may be difficult to interpret, even when slight transmission into the neck occurs, if other evidences of heart disease are not present. These murmurs are best heard in forced expiration. The writer agrees with Scott's statement⁴⁰ that aortic systolic murmurs in adults are so often associated with organic disease that, as a group, it is dangerous to regard them in any other light. Soft systolic murmurs in this area do go unexplained at times, but even then minor changes, rheumatic damage, bicuspid aortic valve, for example, cannot be ruled out. Scott also points out that it is a common error to ascribe systolic murmurs heard in the aortic area to transmission from the pulmonic area. Syphilitic aortitis, aneurysm, arteriosclerotic changes in the aorta, as well as rheumatic aortic disease, may produce systolic aortic murmurs. They may occur at times in the absence of disease, especially in the overactive heart characteristic of such conditions as hyperthyroidism and anemia. In hypertensive patients, also, systolic aortic murmurs may develop. Such a patient may have to bend forward in the sitting position and exhale in order to bring out the murmur. It is evident, therefore, that disease in the region of the aortic valve may, and often does, produce soft, blowing, localized systolic murmurs which, had they occurred in the pulmonic area, would be disregarded. Such a murmur raises the suspicion of disease long before a thrill, musical or harsh quality, transmission to the neck, or changes in the second sound, develop.

The patient's age is of importance in the evaluation of aortic murmurs. In infancy—rheumatic fever and congenital heart disease; in middle age—syphilis and rheumatic fever; and in advanced age—arteriosclerotic changes in the aorta or in the cusps or ring, should be considered. Systolic murmurs of aortic origin may rarely be heard best at the apex; and there are several patients on record in whom aortic disease has produced apical murmurs, at times even with a thrill. Such circumstances are unusual and when aortic murmurs are heard at the apex the intensity is usually greater in the aortic area.⁴⁶

Since the criteria for the establishment of the diagnosis of aortic stenosis by physical means demand a systolic murmur, a thrill and characteristic changes in the pulse, this diagnosis is often not made because of the lack of criteria when the condition is present. With systolic aortic murmurs, this diagnosis is always to be considered and, in the absence of a thrill, changes in the second sound, modifications in the pulse and cardiac enlargement, the systolic murmur may be the only early sign. Under such circumstances, fluoroscopic examination to determine the presence or absence of calcification in the aortic leaflets may be the only means of establishing a diagnosis.

Systolic *tricuspid* murmurs are usually physiologic and intravascular. Organic disease of this valve is rare, whereas systolic murmurs in this region are common. Its ring, for instance, dilates easily with exercise. This occurs so constantly in normal individuals that one would hesitate

to call such dilatation pathologic. The same is true in pregnancy and other states causing increased metabolism. In the cardiac dilatation of disease, a murmur in the tricuspid area is common. Usually the murmur is not conducted widely and has a soft and blowing character.

Systolic *apical* murmurs create the greatest problem in diagnosis because of their frequency and the difficulty in the elimination of the possibility of organic mitral regurgitation.

We have already discussed such characteristics of systolic murmurs as masking of the first sound, transmission, duration and intensity. Constancy of the murmur is known to affect its significance. Definitely pathologic murmurs are often constantly present and little affected by respiration, position and other factors such as tachycardia, which may increase the intensity. Murmurs that are constant from beat to beat and day to day are likely to be harsher, longer and better transmitted. When they are inconstant, they are more likely to be blowing, less intense, localized and heard most often with the patient lying down. The quality and pitch of such murmurs, that is, the presence of harshness and the musical quality,⁸ add some weight to the interpretation of the murmur. However, all of these characteristics do not absolutely differentiate physiologic from pathologic murmurs, for it has been established that all the characteristics ascribed to pathologic murmurs may occur at times in the physiologic group. The rare occurrence of loud, transmitted murmurs, with thrills in the absence of heart disease, has already been pointed out.

Certain other characteristics have been described in apical physiologic murmurs, for example, the bridge effect. It has been stated that the localized systolic murmur of nervous tachycardia may at times be heard only when the bell of the scope rests on 2 ribs and bridges the intercostal space.²⁵ This procedure, when used on a faint systolic murmur, may make it readily audible, when it is otherwise difficult to hear. However, one sees the same effect in more evident systolic murmurs, including the apical systolic murmur of rheumatic heart disease, a fact which indicates that this effect is one of increased intensity of sound, transmitted through the scope to the ear rather than one of differentiation of physiologic and pathologic murmurs.

Certain apical systolic murmurs can readily be determined not to be due to heart disease. This is often, but not always, true of the physiologic, extracardiac, cardiopulmonary murmurs. Since systolic murmurs often occur in conditions which increase the activity of the heart—nervousness, exercise, fever, for example—correlation of the occurrence and disappearance of the murmur with the development and disappearance of the disturbance producing it, indicates the nature of the systolic murmur.

Rheumatic History. From the description of the above characteristics of murmurs which add weight to the interpretation of the murmur as a pathologic one, the deduction may be drawn that the absence of these characteristics usually gives the implication that the murmur is without significance. An inconstant apical murmur which is not transmitted and not related to the factors just above mentioned is commonly regarded as not important. Obviously this is frequently true, as indicated by post-mortem examination. But such faint or inconstant, apparently physiologic, murmurs may result from disease. Even when the murmur does not result from heart disease itself, it is important to find the cause, if possible, for the condition causing it, hyperthyroidism, for example, may be as important as heart disease. Faint murmurs classified as Grade 1 are found in many normal people, so that their use in diagnosis is not

great. Yet they may be associated with organic disease, such as rheumatic fever, and one may not be able to determine from the characteristics of the murmur whether or not rheumatic fever is the causative agent.

Because 20 to 25% of the people with rheumatic heart disease are unaware of a previous attack of rheumatic infection,⁴⁰ a murmur produced by rheumatic fever may occur without any historical evidence to point to its importance. With a history of rheumatic fever, one must reserve his opinion³⁸ and may not, at one examination or over a period of time, be able to determine whether or not an organic lesion is present. Commonly in rheumatic fever several years may elapse after recovery from the acute phases of the disease¹³ before definite signs of mitral stenosis appear. At times evidences of rheumatic heart disease may disappear and leave the patient with a systolic murmur only, or no findings. In Bland, Jones and White's series, about 30% of individuals who had rheumatic fever in childhood showed no clinical evidence at a period averaging 10.3 years after the episode.^{5,6} In 1000 patients who had had early evidence of rheumatic heart disease in childhood, with such findings as enlargement and mitral diastolic murmurs, 83 (8.3%), at a follow-up after an average of 10 years, showed clinically normal hearts, 30 with faint inconstant pulmonic murmurs, and 53 without any murmurs. A much longer period may elapse with no evidence of disturbance except the systolic apical murmur. Periods as long as 15 years are not uncommon. The usual period is much shorter.

It has been said that one is not usually wrong if he does not diagnose mitral insufficiency, in spite of the presence of a systolic murmur, after a period of several years in which no diastolic murmur has developed and there is no evidence of change of cardiac contour, particularly in the left auricular region, by Roentgen ray examination. In a follow-up study on 100 children with apical systolic murmurs, previously reported by Steur and Finberg,¹⁴ they⁴⁴ found that 30% developed severe organic disease, but only 9% of those with perfectly normal hearts, fluoroscopically, developed further evidence of heart disease. In 33 followed over 10 years, 27% developed serious valvular diseases, 61% still had systolic murmurs and 12% none. Blumenthal,⁷ in a group of patients with systolic murmurs and no associated disease detectable by physical examination, electrocardiography, Roentgen ray examination and laboratory studies, but including those with a history of rheumatic fever, followed up 72 of 100 patients for an average of 7 years. A murmur occurred at the apex in 44 and at the base in the remainder. Only 4 cases, after 7 years' follow-up, developed definite heart abnormalities besides the systolic murmur. He concluded that, if the heart is normal in size and rhythm and there is no sign of organic heart disease, the heart is perfectly normal and that, with other evidences, opinion should be based on other signs and not on the murmur.

However, since systolic murmurs may be present for a number of years without the development of mitral stenosis, a history of rheumatic fever would imply that one could not be assured of the absence of mitral valvular disease in such patients. Even when the murmur is slight and has the characteristics that are commonly ascribed to physiologic murmurs, the patient may carry on a normally long and active life without heart failure or other cardiac impairment. This may be true even when the patient has loud systolic murmurs. The ability to carry full activity and lead a normal, active life does not mean that changes in the valve have not taken place. Under such circumstances, however, it is not necessary to restrict

the patient's activity. The unnecessary production of cardiac neuroses and the wrecking of the happiness of many patients has been brought about by such restrictions. Yet the danger of the development of subacute bacterial endocarditis is evident. Experience indicates that in some of these patients with a systolic murmur, at times having only the characteristics commonly considered physiologic, termination in subacute bacterial endocarditis has shown the real significance of the murmur and the presence over a period of years of minimal rheumatic change in the valves.

Past teaching has emphasized that mitral regurgitation from rheumatic valvulitis is rare without mitral stenosis,¹³ particularly after several years have elapsed during which time mitral stenosis is likely to develop. Cabot taught that mitral regurgitation without stenosis was never a justifiable diagnosis. This view would interpret apical systolic murmurs resulting from rheumatic fever as of no consequence, when they frequently are significant.

Since diagnosis on a single sign is never satisfactory and may be impossible, Lendon²³ has stated that, to recognize mitral disease by means of a systolic murmur, it is first essential to eliminate all murmurs which do not arise from the mitral valve and, next, to distinguish between the murmur of a diseased ventricle and that of a diseased valve. For any degree of certainty under such circumstances, a long, harsh, systolic murmur that is transmitted to the axilla must be heard in a patient with a past history of rheumatic fever. Many feel that, if an organic lesion is diagnosed in the mitral valve, stenosis is likely present even though the murmur of mitral stenosis is absent. Diagnoses of rheumatic mitral disease can be, and are, made under certain circumstances in the absence of the diastolic murmur. There is described a widely patent mitral valve with marked regurgitation producing auricular and right ventricular enlargement in the absence of stenosis, as seen postmortem. This is a rare occurrence.

Rheumatic mitral insufficiency cannot be eliminated in a patient with a systolic apical murmur in the presence of a history of rheumatic fever, despite the fact that 2, 5 or even 10 or more years have elapsed, or even when there is no history of rheumatic fever. Such a patient with a systolic murmur may live out his normal expectancy of life, or findings may remain stationary for a number of years and then subacute bacterial endocarditis may develop. Certainly in the absence of a murmur, valvular damage is extremely unlikely. In the presence of a murmur having the characteristics described for physiologic murmurs, the likelihood of organic disease is not great. With the other characteristics described supporting importance of the murmur, particularly with increased intensity and the changes which result with it, the likelihood of the significance of the murmur, even in the absence of enlargement of the heart, is much greater. The arguments for the presence or absence of "pure" mitral regurgitation of a rheumatic origin without some degree of stenosis^{12,23} are of little practical importance, for the systolic murmur alone may be evidence of rheumatic heart disease and may be the only auscultatory sign for many years. It is difficult, even after death, to deduce from the appearance of the cusps whether or not leakage occurred in life.

It must be remembered that the diastolic murmur of mitral stenosis is not always easily heard. It may require exercise of the patient or inhalation of amyl nitrite to bring it out and it may be inconstant. If it cannot be heard, fluoroscopic study of the heart may show changes in the left

auricle and, with the electrocardiogram, help in diagnosis. Calcification of the valves may also be helpful, and in the mitral valve Sosman considers it diagnostic.⁴² Such evidences often may point to the importance of a systolic murmur in the absence of any other findings.

Mitral Incompetence. Regurgitation of blood due to incompetence of the mitral valve may result from any lesion which increases the size of the left ventricular cavity and causes either increased tension of the chorda tendineæ, so that the valves cannot close properly, or dilatation of the mitral ring, producing the same effect. In older individuals with arteriosclerosis there may be thickening and sclerotic changes in the mitral cusps which also might produce regurgitation of blood. In arteriosclerotic disease without cardiac enlargement, a systolic murmur frequently occurs.³⁶ This is particularly true after episodes of coronary thrombosis and some feel that infarction may produce localized dilatation in the mitral ring resulting in the murmur. These findings are likely to develop in older individuals with other evidences to indicate the type of disease, or individuals with obvious types of heart disease, other than rheumatic, with heart failure producing cardiac dilatation. The same finding may occur, as already stated, in anemia with dilatation of the heart. Systolic murmurs almost invariably accompany enlargement of the heart. Thus the factor of age again enters into evaluation of the systolic murmur. Scott⁴⁰ feels that the systolic murmur in the patient over 40 should always be suspected as a sign of heart disease. It is evident that one cannot wait for cardiac enlargement to interpret systolic murmurs as resulting from cardiac disease in older individuals. Diagnosis must often rest upon the presence of the cause for the cardiac changes, or upon the basis of the demonstration of calcifications in the valve cusps. The systolic murmur in older individuals, then, may be the only physical evidence of possible damage to the heart by arteriosclerotic disease, and may be the bit of evidence which leads to electrocardiographic and fluoroscopic studies which confirm the presence of myocardial damage.

Systolic Murmurs in Children. The high incidence of systolic murmurs in infants and children has received some consideration in the pediatric literature. Siemsen^{41b} points out that the literature concerning physiologic murmurs in older children is fairly extensive but in infants is rather sparse. Explanation of murmurs in infants often entails a discussion of the fetal circulatory structures and of anemia. He quotes Jacobssohn¹⁸ as voicing the opinion that non-organic murmurs are not encountered until after the third year of life. Siemsen examined newborn infants at least twice a week during their hospital stay and found a wide variation in the incidence of murmurs. On one day none was heard in 16 infants and on another 5 of 18 showed murmurs. At times murmurs were inconstant during the examination, as well as from examination to examination. In 26 of 105 (25%) murmurs were heard. The figure increased with the number of examinations per patient; and of those examined once, 12% had murmurs; of those examined twice, 15%; and of those examined 3 times, 37% had murmurs. These murmurs were systolic, mostly soft and blowing and usually loudest over the apex. Occasionally they were loud and at times musical. These findings spoke against the murmurs arising from patent ductus arteriosus or patent foramen ovale where they would likely be basal and of a different quality. No extracardiac causes for murmurs were found. Lyon, Rauh and Stirling,²⁷ in a similar study, also concluded that patent ductus arteriosus or patent foramen

ovale usually did not produce murmurs at this time. In 7673 newborn infants, they found only 147 (1.9%) as contrasted to the 25% reported by Siemsen, with murmurs in the first week. In older children, physiologic murmurs, as already stated, are common.

Insurance Statistics. Insurance statistics on systolic murmurs show some enlightening data that should be reviewed by all clinicians interested in cardiac examinations. The insurance approach evaluates mortality in a group. McCrudden³¹ points out that it may seem odd to the clinician that insurability is based upon murmurs rather than upon a pathologic diagnosis. Where the latter is possible, it does form a basis, but with systolic murmurs the characteristics of the murmur are better established and make a more reliable grouping than do the varied diagnoses inferred from these murmurs by the clinician. In such groups the average mortality is established so that outcome for the group is known and can be predicted, whereas the outlook for any one individual in the group cannot. Clinical medicine deals with the individual, insurance medicine with the group.

Standard risks include those people with no impairment, or with minor ones, accepted at regular premium rates. Substandard risks include impairments of a more serious nature to which some restrictions or extra premium are added. A relative mortality of 150% means 50% above normal, or standard mortality, or an extra mortality of 50%.

Most of the figures quoted on systolic murmurs are based largely upon the medical impairment study (M.I.S.) of a group of companies^{1,17,26,31,43} along with some accessory data.^{1,15,17,26,43} A decrease in life expectancy has been found with apical systolic murmurs. In persons with an inconstant systolic apical murmur, not transmitted, the mortality was 135%, or an extra mortality of 35%; with a constant murmur, it was 156%. Hence some portion of this group includes murmurs of organic disease. For systolic murmurs in the pulmonic area the figure is only 112%, indicating that murmurs in this area are largely physiologic. When one adds characteristics which clinically are known to increase the importance of the murmur, for example, the constant systolic apical murmur transmitted to the left (but without a history of rheumatic fever), the figure increases to 224%. The mortality is over twice that expected, indicating that such a murmur is a serious impairment. If one adds moderate cardiac hypertrophy, the mortality becomes 476%, or an extra mortality of 376%. Without enlargement, a history of rheumatic fever, or chorea, or other infectious disease runs the extra mortality up to 229%, and with hypertrophy also, to 365%. Mortality is also greater under similar circumstances in heavy workers than in the white collar class. Tonsillectomy seemed to make no difference.

The above figures are, of course, from those presenting themselves for and obtaining insurance, either at standard or substandard rates, and not from the selected type of clientele which would present itself to the cardiologist for check-up. Interpretation of the results is not influenced greatly by arguments that physicians of varied abilities have built up the groups, for the same factor enters into the control series. The figures confirm the clinical discussions of systolic murmurs already given. Pulmonic systolic murmurs without reliable signs of heart disease are so commonly physiologic and so rarely pathologic that one may individualize with the group data and consider such murmurs as generally unimportant in the

individual patient. However, with apical murmurs, even the inconstant ones having characteristics ascribed to physiologic murmurs, the increased mortality indicates that patients with organic heart disease have been included. This fits in with the reluctance, expressed in the clinical discussion of these murmurs above, to accept them as meaningless even though a great or greater portion may be. Such patients are entitled to all the means we have available, electrocardiography and fluoroscopy particularly, to establish a diagnosis, if possible, not with the object of controlling activity or imposing restrictions which may do the patient more harm than good; but with the idea of recognition of the possibility of future bacterial endocarditis, even though remote in time or frequency. Spaced examinations, intelligently advised for the recognition of further progress of findings to a point where satisfactory diagnosis is possible so that early treatment may be instituted if necessary, also result from such a plan. Certainly the statistics also indicate that when the characteristics of murmur transmission and rheumatic history are added, such a plan as just stated becomes imperative. The addition of hypertrophy of the heart places the patient in a category of definite diagnosis and indications for management become immediately apparent.

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NEUROLOGY AND PSYCHIATRY

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PSYCHONEUROSES IN MILITARY PERSONNEL

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THE neuroses which occur in military personnel will be considered in this paper under the following topical headings:

1. Scope of the Problem.
2. Clinical Syndromes.
 - The Traumatic Neuroses.
 - Other Psychoneuroses.
3. Factors Which Tend to Precipitate a Psychoneurosis in Military Personnel.
4. Psychopathology of Neuroses in Military Personnel.
5. Treatment.
 - Prophylaxis.
 - Induction Center.
 - Establishment of Morale.
 - Need for Prompt Therapy.
 - Therapy of the Acute Neuroses.
 - General Measures of Therapy.
 - Special Procedures and Techniques.
 - Group Psychotherapy.
6. Prognosis.
7. Results of Treatment.
8. Rehabilitation of the Neurotic Service Man After Discharge.

1. **Scope of the Problem.** Psychoneurosis occurring in military personnel was recognized as a major problem in military medicine in World War I⁸⁵ and has grown in importance with the progression of the present war.^{2,47,50,52} Miller,⁸⁷ Kardiner,⁶² Gillespie³⁸ and, more recently, Mira⁸⁸ have dealt intensively with the problems attendant with psychoneuroses in wartime. The monograph by Kardiner⁶² stresses the chronic traumatic war neuroses and has given us a careful study of these cases from World War I. The book by Miller and his collaborators⁸⁷ is based to a large extent on World War I experience, as judged by present-day concepts. Mira⁸⁸ has written of his work in the Spanish Republican Army. Further, if available, the restricted monograph by Grinker and Spiegel⁴⁶ on War Neuroses in North Africa will be found to contain much valuable clinical and practical material. In general most authors agree that the war neurosis represents a special case of a generalized type of behavior and signifies a failure of adaptation.¹¹³ The primary reagents are the indi-

* Now on active service.

vidual constitution and the environmental set-up of the moment; further, it seems fairly clear that processes resembling conditioning occur in man as well as in experimental animals, and that neurotic states have their own dynamics.¹¹³ The unusual factor regarding war neuroses has not been the type or form of the reaction, since there have been no new clinical entities produced,^{15,50} but it is the fact that this war has demonstrated, in the acute war neuroses, that men who have been considered normal may develop neurotic manifestations when placed under excessive fatigue, strain, or emotional upheaval.^{50,76,91} However, some writers hold that, without a predisposition, circumstances however bad, do not produce a neurosis.^{18,19,47} The tendency toward failure and breakdown has to be regarded quantitatively: in some, it is small and needs considerable stress for its manifestation; in others, it is stronger and becomes manifest on slight stress.^{11,15,47,113} The individual constitution determines the form and severity of the neurosis; the momentary environment determines the time of manifestation and to a lesser extent the severity and even the form of the symptoms. Hypochondriasis, depression and anxiety seem to be of all the neurotic symptoms those most directly related to exogenic factors and those which can be most reasonably regarded as a general human weakness, and there are certain circumstances under which it would be abnormal not to be afraid, or depressed, or preoccupied.¹¹³ Military stress has a special tendency to produce anxiety symptoms and some authors³⁹ feel that the stress can so outweigh the individual personality factors that a heterogenous group of men under the same severe stress can produce remarkably similar symptom pictures.

In the neuroses which develop in military personnel under non-combat conditions, personality factors and predisposition play a large rôle. Careful study of these psychoneuroses reveals that in practically every case the true onset of the disorder took place sometime before enlistment or induction.⁹⁶ And although the men who went through severe stress before developing a neurosis do represent a selection for greater constitutional stability, the signs of a neurotic makeup are still to be found (for example, 45 % of one such group had a positive family history).¹¹³ In a previous paper⁵⁵ appearing in this section, it was possible to cite statistics from several articles on the incidence of positive social history and background data in all neuropsychiatric casualties, combatant and non-combatant, and also in soldiers who broke down only after active duty. The significant factors predisposing to neurotic breakdown are:^{30,55}

1. Age. The older age group showed a higher incidence of neuroses.
2. Previous hospitalization for mental illness or previous treatment by a psychiatrist.
3. Previous antisocial behavior.
4. Poor adjustment in school.
5. Poor occupational adjustment.
6. Positive family history ("broken home," mental illness in immediate family, poor economic status).
7. Cerebral concussion.

In almost all papers^{1,9,18,19,42,43,44,47,57,75,76,90,113,117} the factor of predisposition is considered. The conclusion reached by all was summarized in a statement of the Surgeon-General: The Army is one of the elements of national defense, and its present mission is one of preparation for an offensive-defensive type of warfare. It is in no sense a social service or a curative agency. It is to be considered neither a haven of rest for

wanderers nor a corrective school for misfits, ne'er-do-wells, feeble-minded persons or chronic offenders. Furthermore, it is neither a gymnasium for the training and development of the undernourished or underdeveloped nor a psychiatric clinic for proper adjustment to adult emotional development. Therefore, there is no place within the Army for physical or mental weaklings, potentially psychotic or prepsychotic persons or behavior problems. Men who present behavior problems in the civilian community will certainly present intensified problems in the service.¹⁴

However, there are as yet no definite criteria for the rejection of men suspected of being predisposed to acute traumatic neuroses.¹⁰¹ The most careful studies have not revealed a personality structure common to these cases, and it is our belief that the psychologic mechanisms associated with the traumatic neuroses are so fundamental as to be present in all men; hence, as a corollary, the precipitating force lies in the personality's environment and is thus to some extent controllable.¹⁰¹ The ordinary psychiatric problems of peacetime also occur in the setting of war, and are colored by the war, and here the backgrounds are those of the usual psychoneurosis: childhood insecurity, parental rejection, faulty inheritance, early evidence of maladjustment and immaturity.¹⁰¹

2. Clinical Syndromes. *The Traumatic Neuroses.* It must be stated at the outset that many writers do not agree to the separation of the traumatic war neuroses as a distinct clinical entity considered apart from the psychoneuroses which occur in military personnel under non-combat conditions.^{6,8,14,15,20,21,22,29,47,75,82,92,94,96,105,110,113,119} However, many of the authors who have returned from actual war experience deal with the traumatic war neuroses as a syndrome in which the psychopathology, the prognosis, and, to some extent, the symptoms differ from that of the non-combat psychoneurosis to such a degree as to place this group under separate consideration.^{7,39,56,59,76,91,93,98,114} The article by Raines and Kolb¹⁰¹ and the discussion by Raines¹⁰⁰ state this point of view well. Further, Kardiner,⁶² studying cases of World War I, attempted to separate his cases in a similar fashion.

To delineate this disorder, the combat neurosis, Raines and Kolb^{100,101} listed the criteria for the diagnosis of an acute war neurosis: (1) a stable personality prior to the appearance of the traumatically determined emotional disturbance; (2) a combat experience of sufficient intensity to make it a reasonable precipitating agent; (3) objective evidence of subjective anxiety; (4) good recoverability in even a short period of time (3 months) with relatively superficial therapy. The symptoms of a traumatic neurosis can be summarized to include 4 patterns of reaction:¹⁰¹ (1) The repetitious catastrophic nightmares.^{62,68,79,86,101,105,110} these reenact the traumatic scene, are always accompanied by fear which is often childlike in its emotional pattern, and the effect of the fear persists after awakening. (2) The startle reaction.^{62,68,79,101,105,110,114} sudden loud noises, day or night, produce a sudden start and also physiologic evidence of anxiety—tremor, dilated pupils, sweat, dry mouth, flush or pallor, palpitation of the heart—and may even give an actual panic reaction. (3) Subtle personality change.^{63,79,101,105,110} the patients become morose, silent, sullen, irritable, intolerant of noise or argument, show vacant staring expression, frequently resort to alcohol and frequently are a disciplinary problem; as might be expected, this third symptom is a very variable one. (4) A reaction of guilt accompanied by emotional depression.^{79,101,114} this is frequently, but not always, present; it occurs often in survivors of disaster in which a number of the original group were lost, and, in addition to revealing itself

in depression, the sense of guilt also leads to protestations that nothing could have been done for those lost and to the careful exposition of the survivor's efforts to save others.

A further characteristic of the combat neuroses is the rapidity with which new symptoms appear and disappear.³⁹ It is hard for statistics or classifications to reflect this fluidity of the symptomatology.¹¹³ As time goes on, without treatment, a more stabilized syndrome results. Potter⁹⁸ defines a traumatic war neurosis as a massive explosion of anxiety or fear at a primitive psychologic level, producing a psychosomatic disorganization of the entire organism; it is precipitated by a catastrophic threat to the total organism and preceded by psychosomatic tension and fatigue for a period during which the subject is both consciously and unconsciously poised, mentally and physically, for offensive or defensive action. Psychosomatic disorganization is reflected in symptomatology related to disturbances of the conscious or ego mental functioning; the emotional organization; and those somatic structures dominated by the autonomic nervous system. The autonomic and psychologic disturbances, in turn, provoke secondary anxiety, conscious in nature, thus creating a widespread subjective insecurity which further disorganizes the ego. Finally, the conscious anxiety and generalized subjective insecurity, with its concomitant physiologic and psychologic tension, serves to feed the basic psychosomatic disorganization and to perpetuate the primary physiologic and psychologic disturbances.⁹⁸ Kardiner⁶² states that the traumatic neuroses results from contraction of the executive functions of the ego, and that this involves that aspect of ego functioning which deals with the interpretation and mastery of the outer world; the patients approached any activity with a view in which they appeared utterly helpless and their world dangerously hostile. The traumatic neurosis may be superimposed on the neurotic background but the two conditions are different and can be readily distinguished; later on, in the chronic stages, the two neuroses may become fused and difficult to distinguish but they must still be treated individually in keeping with their respective psychopathologic construction.⁷

Other Psychoneuroses (in which the individual's personality and not combat is the major etiologic agent). Military service furnishes an excellent medium for the growth and development of a psychoneurosis in a susceptible personality.^{14,57,62} The psychoneurosis is thus a pattern of adjustment which the person makes to the problem of living in a military environment and represents a failure of adaptation within the personality which gives rise, owing to emotional conflict, to symptoms which may be of conscious or unconscious origin.^{8,69,91} These neuroses are typical of the neurotic illness seen in civilian life,⁹³ except that anxiety, panic states and reactive depression seem to be more common in the service than in civilian life.^{27,29} There are strong correlations, statistically, between the makeup of the personality and the symptoms exhibited in the neurosis.^{1,113} These psychoneuroses fall into the usual types seen in civilian psychiatry, the most common forms being: (1) the anxiety states, (2) the conversion hysterias, and (3) the reactive depressions.^{13,20,21,39,50,57,74} In order to group the acute and chronic war neuroses in a single classification, Whitehead¹²⁴ used anxiety as the basic factor and arranged the psychoneuroses in 3 groups: (1) neuroses in which anxiety shows itself directly as a symptom (anxiety states, fear states); (2) neuroses that are defenses developed in the individual against the direct manifestation of anxiety (conversion hysteria, compulsions, phobias, hypochondriasis and regressions to earlier childhood patterns of behavior); (3) neuroses which present

the by-products of the struggle between anxiety and the defenses against it (neurasthenia, fatigue states, mild depression).

3. Factors Which Tend to Precipitate a Psychoneurosis in Military Service. Almost every article on the non-combat neuroses stress the rôles played by the individual's own personality background and his constitutional predisposition. However it is universally recognized that military service has inherent factors which tend to precipitate a neurosis. Knight and Orr,⁶⁷ Billings⁹ and Pignataro⁹⁶ have all written excellent articles discussing these factors. In summary, the factors during the training period are:

1. Separation from home ties.
2. Anxiety over home responsibilities and family.
3. Change in habit routines.
4. Necessity of submission to authority and discipline.
5. Loss of prestige and other "narcissistic" blows.
6. Contacts with other men without any privacy.
7. Guilt over feelings of aggression.
8. Exhaustion and monotony.
9. Sex deprivation and sex conflicts.
10. Arousing fears of bodily injury or death.

The precipitating factors in the combat zone are:

1. All of the factors of the training period.
2. Insufficient period of training for combat.
3. Fear of his own cowardice.
4. Disappointments and feelings of frustration.
5. Lack of faith and confidence in leaders.
6. Increased fatigue.
7. Increased responsibility.
8. Poor food and poor sanitation.
9. Exposure to explosions, blast and gases.
10. Effects of climate, and of somatic disease.
11. Repeated narrow escapes following one another in rapid succession.

The articles dealing with these above factors were summarized in this section a year ago,⁶⁵ and since then there have been other articles discussing these factors.^{35,58,62,65,80,101,105,123,124}

4. Psychopathology of Neuroses in Military Personnel. Just as in civilian neuroses, anxiety is the important causative factor in the neurotic illness.^{43,64,96,100,124} However, the emotional conflict producing this anxiety does have certain factors peculiar to the military situation.^{51,80} The following are some of the psychopathologic factors which seem to be important in the causation of anxiety in military personnel:

(a) *The Conflict Between Acquired Social Attitudes and the "Instinct" of Self-preservation.*^{14,41,43,65,105,120} Miller⁸⁷ states that frequently the neurotic patient had stuck to his duty until the controlling force was no longer able to stand up against the insistent demands of an instinct which demanded either an escape from danger or an aggressive outburst. He also considers the rôle of self-love and other emotional conflicts. Williams¹²⁵ feels that there is first a basic personality structure characterized by self-centeredness, overconscientiousness, lack of sociability and lack of affection for relatives and friends. The unconditional demand for self-sacrifice in war means a renunciation of narcissistic privileges which these individuals cannot do. They have a diminished capacity for external interests and emotional ties, and an increased self-centeredness which is expressed in the neurotic illness. As Thom¹²⁰ says, in order to be adequate and to fulfill the purpose of protection for which it is psychologically designed, the neurosis allows the soldier to escape from the intolerable situation

created by impending danger and to accomplish this without loss of self-respect.

(b) *The Traumatic Factor.*³¹ Often the traumatic experience is one which serves to precipitate a psychopathologic reaction through the activation of preëxisting but hitherto latent psychopathologic factors. In certain cases it is possible to detect a very high degree of specificity in the traumatic experience.

(c) *The Factor of Infantile Dependence.*³¹ Fairbairn³¹ feels that there is a close relationship between the development of a war neurosis and the persistence of infantile dependence. This has also been found present in cases of malingering.⁴⁰ The neurotic symptoms are seen as essentially either effects of, or defences against the conflicts attendant upon a persistent attitude of infantile dependence in the emotional sphere. This gives rise to a common basic symptom of separation-anxiety; the soldier becomes ill because he craves to go home. Further, the capacity to endure danger varies with the extent to which the individual has outgrown the stage of infantile dependence. This factor has been recognized also in articles by Flicker and Weiss³⁴ and by McKerracher.⁸³ The latter author⁸³ writes that so active is the protective mechanism of the neurotic that some wag has translated D.A.H. to mean not "disordered action of the heart," but rather, "desperate affection for home." Fairbairn³¹ feels that much of the symptomatology of the neurosis is the expression of the compulsiveness of the desire to return home.

(d) *The Factor of Identification.*³¹ By identification the individual tends to identify himself emotionally with, and *pari passu* fails to differentiate himself from those on whom he depends. The original identification of anyone is with his mother (and later his other parent and parent substitutes). When emotional development is satisfactory, there is a progressive decrease in identification, accompanied by a progressive increase of a capacity on the part of the individual to differentiate himself from emotionally significant figures. Emotional maturity is consequently characterized not only by a capacity to sustain relationships with other individuals on a basis of mutual independence but also by a capacity to contract fresh relationships. These capacities are deficient in the individual who fails to outgrow the stage of infantile dependence. Hence such a person, when placed under military conditions, finds it too difficult to establish himself as a separate personality within the framework of the military organization, subordinate himself to the aims of the military group without any surrender of individuality, and maintain stable emotional bonds with the group while remaining differentiated from it. On the other hand, he also usually finds great difficulty in either establishing or maintaining a reliable relationship with the military group on the basis of identification. This is due, of course, to the fact that his identification with his home and his loved ones proves too strong to admit of a competitor; and it is to the strength of this identification to his home and loved ones that above all the development of a war neurosis must be attributed.³¹

(e) *The Factor of Morale.*³¹ In the case of the "normal" soldier, acute anxiety occurs only when the bonds uniting the group as a whole are dissolved. Each quondam member of the group becomes thus deprived of the support both of his fellow-soldiers and of the military group as a whole, and is relegated to the status of an isolated individual facing the combined strength of a hostile force without any support. Confronted with such a perilous situation, the soldier may be assailed by panic. Thus, even a "normal" soldier may develop a war neurosis, albeit a transient one, in circumstances in which morale becomes impaired. Further,

the existence of a high state of morale within a group can exercise a profound influence in counteracting the ill-effects of infantile dependence among its members. However, in the case of a neurotic soldier, separation-anxiety may occur even when the bonds uniting the group as a whole remain intact. This means, of course, that the bonds uniting the neurotic soldier to the military group are unduly slender and precarious, because he has retained from childhood an excessive degree of infantile dependence.³¹

(f) *The Super-ego Factors.*³¹ Once the neurosis is established there is a remarkable absence of guilt over the evasion of military duty involved. The only exceptions to this are in cases with depressive and obsessional features; and in the prodromal stage of the war neurosis, where there is still real conflict between the desire to return home and the sense of duty. What happens is that the neurotic soldier regresses, in a greater or lesser degree, to a level of infantile development at which the structure of conscience has not yet been organized on a stable basis. The neurotic soldier is thus more or less reduced to the emotional state of a child who has not yet reached the stage of accepting his parents as authoritative conscience-figures and hence he does not regard the military organization as an authoritative parental figure to whom he is bound by a deep sense of moral obligation. Rather, he begins to regard his officers as "bad" parental figures who have no love or consideration for him. At the same time he identifies those at home as "good" parental figures who love him and who will look after him if he can only get back to them. Thus he becomes consumed by an overwhelming desire to escape from the insecurity which he experiences at the hands of the "bad" figures—into whose clutches he feels that military obligations have delivered him—to the security which the "good" figures at home seem, by contrast, to offer him.³¹

Treatment. In order to treat any patient successfully, whether in civilian or military life, the physician must first understand his own emotional attitudes and conflicts; in order to help the physician clarify his feelings upon entering military life, Menninger⁸⁴ has discussed some of the problems in adjustment which he will meet. Further, there are many articles which survey the general administrative duties of military psychiatry,^{24,45,49,54,97} and others which stress the prophylactic value of a competent neuropsychiatric examination at the Armed Forces Induction Center.^{54,55,74,75,77,126} The factors leading to the establishment of good morale have been considered and the following have been found to be important.^{23,33,67,73,74,75,79,80,81,89,101,118,119,122}

1. Adequate training in order to develop confidence and skill.
2. Prevention of fatigue and monotony.
3. Keeping the men occupied either in constructive play or useful training.
4. Giving the men some degree of psychologic self-understanding regarding the problems of fear, sex and war motives.
5. Classification of men to duties chosen according to the mental and emotional capabilities of the individual soldier.
6. Elimination of men with manifest personality disorders.
7. Establishment of group morale by appreciation of and faith in the ideals and goals for which the war is being fought, by setting up clear and simple common goals of personal significance to each soldier, by stressing positive and not negative drives: love and ideals, not fear and hate.
8. Provision of adequate diet, rest, medical and personal care and recreation.
9. Establishment of identification with the group, and loyalty to it and the officers.
10. Personal interest in the men by the officers.
11. Instruction in psychiatry for general medical and line officers.

The use of a mental hygiene, or special training, or rehabilitation unit can be of great value when it is properly established and when the staff includes psychiatrists, psychologists, vocational guidance officer, occupation therapist, and psychiatric social workers.^{35,36,57,104,118,128} Further, the establishment of an out-patient psychiatric service, an adequate consultation service, and a Barracks psychiatrist are all worthwhile prophylactic measures.^{36,128}

When we concern ourselves with the actual treatment of a neurosis in military personnel the first axiom, and an important one, is to treat promptly and as near the site of the inception of the neurosis as is feasible.^{5,39,56,67,89,91,102,120} The second rule is to separate the neurotically ill soldier from his healthy comrades as soon as possible in order to maintain group morale.^{5,17} The third basis of treatment is that the length of stay in the combat-zone hospital is kept as short as possible (2 to 21 days),^{91,120} in order to prevent the fixation of the protective mechanisms and the development of the neurotic personality pattern.^{17,39} Likewise the medical officer expresses optimism and coöperation but is not too sympathetic (stern kindness) and he establishes some form of work program as soon as possible.^{5,91}

As to the actual therapy which should be carried out promptly on the acute combat neuroses, there are two basic principles: (1) the giving of complete physical and mental rest;^{15,17,50,59,66,68,98,101,106,107,108,109,125} (2) the restoration of normal body metabolism and nutrition.^{17,50,59,66,68,98,108,109,125} The rest is given in bed, with maintenance of adequate bodily warmth, and with sedation in sufficient amount to secure deep sleep of at least 10 hours' duration and sometimes extending for 48 hours.¹⁰⁹ Sedatives which are used are the intravenous barbiturates, or paraldehyde by mouth or rectum, or sodium amytal by mouth.^{66,108,109} This deep sleep is often followed by 1 or 2 days of milder sedation.¹⁰⁸

The normal body metabolism and nutrition is restored by use of food and fluids in large amounts, the use of intravenous fluids and plasma.^{66,109} If necessary, continuous sleep treatment can be used also.^{68,109} An important factor is weight loss and progress can be judged by its restoration.¹⁰⁹

After the patient has recovered from his exhaustion, then the psychotherapeutic measures can begin: these include in the early stages the use of reassurance and support,⁶⁶ catharsis,^{28,47,66,68,101,107} hypnoanalysis^{32,47,66,68,127} and narcoanalysis.^{4,32,47,66,68,127}

Catharsis allows for emotional desensitization of the patient to the traumatic experience, and regardless of the improvement gotten by rest, this desensitization should be begun immediately thereafter.¹⁰¹ It consists simply of encouraging the patient to tell of his combat experience in an atmosphere of mutual understanding and respect.¹⁰¹ It gives release from obsessive waking nightmares, from obsessive guilt feelings and from rage; it allows a return to the sensations of real life.⁶⁸ If hypno-narcoanalysis is used, it is done for a fourfold purpose: (1) to allow the patient to express feelings of which he may be dimly aware yet afraid to express; (2) to allow the patient to become aware of feelings which he may have buried so completely as to be totally unaware of them but which may nonetheless disturb him; (3) to allow the patient to express these deeply buried and unconscious feelings; (4) to penetrate into the amnesic areas of the patient's psychologic processes in order to "waken" that aspect of the personality and those mechanisms of control which were rendered inaccessible by the traumatic experiences.⁶⁸ The recovered material must be fully fused with its appropriate emotional content and with normal waking consciousness;⁶⁸

it is indispensable for cure that the dissociated or repressed thoughts be brought into consciousness after the resistances have been broken through.^{4,32,47,66}

After the patient has been evacuated from the combat zone, certain other psychotherapeutic measures can be utilized along with the above-mentioned ones. Up to this point in the treatment the primary aim of therapy was to restore the patient to combat duty; now the primary aim becomes one of rehabilitating the patient for civilian life in a productive capacity.⁶⁶ Treatment now proceeds with a carefully taken psychiatric history and a complete physical and mental examination, including psychologic testing, so that a proper evaluation of the patient's capabilities can be made.^{66,125} If possible, a social history¹²⁸ with report of the patient's pre-war personality and adjustment are included.^{24,76} The patient is encouraged to give the onset and development of his illness in utmost detail, and this often serves as an opportunity for an out-pouring of pent-up emotions.^{2,121} In the treatable cases, active psychotherapy is carried out by attempting to explain the nature of the illness to the patient. An endeavor is made to concentrate the patient's attention on the fact that his state is the result of normal fear in a sensitive individual, and that in his endeavor to control that normal fear by calling up forces by sentiment, self-respect, social tradition, or morale, he has displayed courage rather than cowardice. Care must be taken not to appear too sympathetic and while reassurance and explanation are helpful, the patient must be made to realize that he is expected to recover and that ultimately he himself must climb back to the manhood level from the infantile level to which he has, for the time being, regressed.^{2,51,61} Further, occupational therapy,¹¹² vocational training and educational training are all useful tools.^{2,24,66,76,127} Recreational therapy through both individual and group games and sports is of value,^{66,127} this recreation should be largely the result of the patient's own efforts (a concert by patients is better than a movie).²⁴ In those patients who are not accessible to ordinary psychotherapy, shock therapy is used: electric shock therapy,^{108,109} modified insulin therapy,^{108,109,126} and the usual insulin treatment.⁶⁶ Often the shock therapy is discontinued as soon as the patient becomes accessible to direct psychotherapy.^{5,107} Sometimes many of the phenomena of the acute war combat neuroses appear to be acute states of partial dissociation, which precipitate the patient into a waking nightmare from which he cannot be aroused; such patients can be made accessible to contact by insulin therapy or electric shock treatment and the methods should be used as soon as the state is recognized and before it becomes chronic.⁶⁸ In the excitements, prolonged sleep under continuous narcosis may be helpful,^{68,109} although the results have sometimes been disappointing.¹⁷ The sleep must be deep so that it is not disturbed by nightmares or obsessional horror reveries, and it is sustained for several days, maintaining at least 20 hours sleep in each 24-hour period but allowing the patient to be roused for meals, fluids and elimination.⁶⁸ Psychoanalysis of a war neurosis is used but it should not be undertaken unless one is prepared and competent to complete the therapy and to unearth the nucleus of the underlying, formerly latent psychoneurosis.⁵

The use of group psychotherapy is becoming more and more prevalent in the treatment of the war neuroses,⁵⁹ and seems to be applicable to a large per cent of the cases.⁵³ Several fairly comprehensive articles have appeared on this method of therapy.^{10,12,53,60,115} and the exact technique used varies with each author. There is a general agreement in the litera-

ture that individual psychoanalytic procedures do not fulfill all the therapeutic needs of the patient;^{59,68,100,105,111} all those problems and conflicts which come roughly within the domain of the social super-ego do not seem to get properly worked out.¹¹¹ One of the main distinctions in treatment implied in group therapy is the introduction of a didactic element.¹¹¹ The basic plan for a group therapy program consists of: first, preliminary diagnostic and therapeutic interviews with each individual patient; then a course of several lectures given to the group by the physician during which various methods of participation by the group in the discussion are used; individual interviews given to most of those patients who do not show satisfactory improvement during group treatment.

Prognosis in the Neuroses Occurring in Military Personnel. There are several factors which favorably influence the prognosis in the war neuroses:

1. The sounder the integration of the premilitary personality, the better the prognosis.¹¹⁹
2. The more severe and continuous the combat experience before the break occurs, the better the prognosis.¹¹⁹
3. The more marked the exhaustion, deprivation, and in general the somatic factors, the better the prognosis.¹¹⁹
4. Prognosis is better in the anxiety neuroses and conversion hysterias than in the neurasthenic-hypochondriacal states and the obsessive-compulsive reactions.¹¹⁹
5. Prognosis is better when the man has a certain period of time in which to "digest" the emotional turmoil of one traumatic experience before being exposed to another.¹⁰¹
6. Prognosis is better when the psychiatrist is able to transfer a man from one unit to another on psychiatric grounds, to arrange his allotment to duties particularly suited to the man, and to recommend him for a station in the neighborhood of his own home.^{25,113}

The prognosis in the neuroses of war is unfavorably influenced by the following factors:

1. The longer the time elapsing between the occurrence of the casualty and the initial psychiatric aid, the worse the prognosis.¹¹⁹
2. Beyond a certain area, the farther a casualty is removed from the zone of combat, the poorer the prognosis.^{101,119}
3. All symptoms are liable to be aggravated in the presence of loved ones, friends, relatives, spouse, or family. In such a situation the traumatic anxiety attaches to the emotional ramifications of family life and may become irreparably fixed.¹⁰¹
4. The prognosis is poorer if the "war neurosis" becomes incorporated with any underlying emotional conflict, or mental deficiency, or incipient psychosis, or organic brain damage.¹⁰¹
5. The prognosis is poorer in patients with a poor heredity, or with unfavorable personality traits before service, or with constitutional predisposition, or with difficulty in adjustment prior to service, or with strong resentment of military service.^{71,91}
6. Recovery is consciously or unconsciously resisted, since this means a return to the rigors of duty.³
7. Treatment is free; a patient makes no financial sacrifice; he need contribute nothing toward his cure; therefore, the treatment has "no value" to him.³
8. It is difficult to effect a permanent or personal relation between physician and soldier because of frequent change of station by both. A feeling of permanence or a sense of follow-up responsibility is missing.³

9. A patient goes through the hands of many different physicians and their varying points of view.³
10. The soldier feels he is being treated by the same agency responsible for his plight.³
11. Negative suggestion by other patients.³
12. The presence of secondary gain in the illness through pensions and compensation which continue in effect so long as and only if the neurosis continues.^{3,22,66,72,79} If any compensation is given to neurotic patients it should be on a one-lump-sum basis.

Results of Treatment. The statistics on the per cent of the various types of psychoneuroses who return to full duty or are returned to limited service are probably unavoidably unreliable because psychiatrists in the forward area and even in the general base hospitals have almost no opportunity to follow up their cases with sufficient accuracy and over a long enough period of time.⁷¹ Further, it is difficult to judge the therapy on the basis of the per cent returned to duty because it depends greatly on the type case with which the psychiatrist is working. However, in Table 1 we have compiled the results of treatment as given in the literature. In addition, Smith¹¹⁴ reporting on cases from Guadaleanal said that very few of the patients would be able to return to combat duty and only 10 to 15% would be able to return to limited duty. Sutherland²⁶ in 1941 reported only 9% of his patients as fit to return to full duty after treatment at a neurosis center. In contradistinction to this, we have had recent reports of 60%, and even 75% of the war neuroses treated in the combat zone returning to duty.¹⁰⁵

Rehabilitation of the Neurotic Service Man After Discharge From Service. There have been encouraging steps taken toward the handling of this problem within recent months. The formation of a Division of Rehabilitation by the National Committee for Mental Hygiene, and the increasing awareness of the United States Employment Service in this problem, and the formation of rehabilitation clinics in New York and Massachusetts, with plans for other such clinics in Wisconsin, Connecticut, Vermont and Colorado—all of these are extremely favorable signs. However, there exists a need for national planning for psychiatric rehabilitation and this is the service which Rennie is beginning to supply.¹⁰³ The Barden-LaFollette Vocational Rehabilitation Amendment was approved by the President on July 6, 1943, and makes the mentally disabled, as well as the physically disabled, eligible for rehabilitation.¹⁰³ Rennie¹⁰³ feels that there are 5 major needs existing in regard to adequate psychiatric rehabilitation; these are: (1) the scarcity of psychiatric help available; (2) the time-lag between discharge and beginning of treatment; (3) the need of a total psychiatric and physical survey for these men; (4) the need for community coöperation in this endeavor; and (5) the need for a closer liaison relationship with the Army and the rehabilitation agencies.

The rôle of the psychiatric social worker in rehabilitation is a major one and has been recognized.^{48,128} There have been a few articles^{97,120} in the literature on a rehabilitation program for the discharged soldier; those by Sommer and Weinberg,¹¹⁶ Rieckles,¹⁰⁴ Preston⁹⁹ and Pratt⁹⁵ are good. That the soldier discharged on account of neurotic illness needs such a rehabilitation program is shown by the English survey which revealed that in 120 soldiers discharged with a diagnosis of psychoneurosis, 50% had made an unsatisfactory social adjustment in civilian life;⁷⁰ further, 12% of them were unemployed and 51% of those employed earn less than they did before enlistment.⁷⁰

TABLE 1.—RESULTS OF TREATMENT OF NEUROSES IN MILITARY PERSONNE

Reference No. and Date	Type of neurosis	Improvement				Disposal			Follow up	
		None (%)	Slight (%)	Great (%)	Recovery (%)	Return to duty (%)	Trans- ferred (%)	Inva- lided (%)	No. observed	Success (%) Failure (%)
113 Jan. 1943	Anxiety neurosis	14.6	42.5	33.2	9.7	26.5	1.0	72.5	122	52.5 47.5
	Hysteria	17.7	40.9	20.0	15.4	25.2	3.1	71.7	77	50.7 49.4
	Reactive depression	16.6	39.0	31.6	12.7	22.3	2.8	74.9	40	60.0 40.0
120 World War I	All types of psychoneuroses	65.0	30.0	5.0		
7 July 1943	Traumatic neurosis	9.0	42.0	30.0	19.0	57.0	16.0	27.0		
75 Aug. 1942	Hysteria	44.4	..	55.6		
	Fear or anxiety states.	55.8	..	44.2		
5, 24 Aug. 1942	War neurosis treated in combat zone	60-65	20-25	10.0		
5 Sept. 1941	War neurosis treated in hosp. in interior	20.0	15.0	65.0						
25 Dec. 1940	All types of psychoneuroses	33.0	67.0			
24. Aug. 1942	All types of psychoneuroses	61.0	23.0	12.0		
	Hysteria	77.0	20.0	3.0		
	Anxiety states	55.0	30.0	10.0		
75 Aug. 1942	Hysteria	44.4	..	55.6		
	Anxiety states	55.8	..	44.2		

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PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF MAY 16, 1944

Factors Affecting the Determination of Oxygen Capacity, Content, and Pressure in Human Arterial Blood. F. J. W. ROUGHTON, R. C. DARLING, and W. S. ROOT (Fatigue Laboratory, Harvard Univ. and Dept. of Physiology, College of Physicians and Surgeons, Columbia Univ.). The percentage saturation of the arterial blood is usually obtained by dividing the O_2 content, as determined gasometrically, soon after the sample is withdrawn, by the O_2 capacity determined some time (often an hour or more) later. We have no changes to suggest in the Van Slyke determination of O_2 content, but we have found 3 factors all of which cause the oxygen capacity of blood, as determined by the usual method of rotation with air in a tonometer, to be greater than its presumed value *in vivo* before withdrawal from artery or vein:

1. The blood which drains to the bottom of the tonometer, when this is stood up for withdrawal of the sample for analysis, contains a slight excess of hemoglobin, owing to the fact that plasma sticks to the walls of the vessel better than do red cells. This has been proved by direct analysis of the Hb and total N of the dregs.

2. Normal human blood (especially that of smokers) contains traces of COHb, which dissociate to a very slight extent during rotation with air. The effective O_2 capacity hence increases correspondingly. Under average conditions these 2 factors cause a total apparent increase equal to about 0.8% of the total capacity.

3. Reversion to normal hemoglobin of some of the 3% (average figure) inactive fraction of hemoglobin established to be present in normal human blood by Ammundsen (*J. Biol. Chem.*, **138**, 563, 1941) and ourselves. The extent of the reversion varies unpredictably but averages 1 to 1.5% of the total hemoglobin.

The sum of the 3 effects would be expected to be about 2%, which would raise the average figures for the per cent O_2 Hb in arterial blood from 95 to 97, at sea level. The pO_2 corresponding to 97% O_2 Hb is 98 mm., if read off from a standard dissociation curve; this value is very close to the average figure for the alveolar pO_2 of normal man at sea level. We believe that the previously claimed differences of 20 mm. Hg between alveolar air and arterial blood at sea level are in error, through inattention to these 3 factors. In view of the difficulty of allowing for these factors satisfactorily in given instances, it seems doubtful whether the continued use of the dissociation curve for determining arterial pO_2 at sea level is desirable; this caution does not, however, apply to experiments at altitude, where the per cent O_2 Hb is below 85, since in this range an uncertainty of 2% O_2 Hb only affects the determination of pO_2 to the extent of 2 to 3 mm. For sea level determinations of arterial pO_2 it would seem that wider use should be made of aërotonometer methods.

Owing to the smallness of the reversion effect we have as yet no data as to the nature of the hemoglobin compound involved (*c. g.*, is it in whole or in part methemoglobin?) nor do we know how it varies in exercise, acclimatization to high altitudes and pathologic conditions.

Spectrophotometric Observation of Circulating Blood in Vivo, and the Direct Spectrophotometric Determination of the Saturation of Hemoglobin in Arterial Dog Blood.* DAVID L. DRABKIN and CARL F. SCHMIDT (Depts. of Physiological Chemistry and Pharmacology, Univ. of Penna.). Uncertainty exists at present concerning the degree of saturation of arterial blood at sea level. The usual gasometric technique for determining the percentage of saturation of hemoglobin with oxygen is indirect. Two separate analyses, *oxygen content* and *oxygen saturation*, are required. (*Oxygen content/oxygen capacity*) $\times 100$ gives *percentage saturation*. Several criticisms of this procedure may be made. Uncertainty in *percentage saturation* of arterial blood leads to uncertainty in the value of its *oxygen tension*, usually read off from previously determined oxygen dissociation curves, which relate saturation to tension. The portion of the dissociation curve which applies to arterial blood at sea level is asymptotic, so that 2 to 3% difference in saturation corresponds to a difference of 20 to 30 mm. in oxygen tension. In seeking additional information upon arterial saturation, we have turned to the spectrophotometric analysis of arterial blood. The optical technique is particularly appropriate for the direct quantitative determination of 2 or more species (in the present work, HbO₂ and Hb) in a solution.

* Work done under contract with the Office of Scientific Research and Development.
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The continuous direct spectrophotometric observation of circulating blood *in vivo* has been successfully carried out. For this purpose the Drabkin and Austin special cuvette of 0.007 cm. depth was used. The cuvette was intercalated in the femoral artery of nembutalized dogs, arranged upon a board beneath the optical bench of the spectrophotometer. Clotting was prevented by previous intravenous injection of Pontamine Fast Pink and periodic injection of heparin.

A homogeneous circulation of the diverted blood flow through the very thin cuvette chamber was maintained, permitting visualization up to periods of 4 hours. The passage of blood through the cuvette was pulse-like in character (synchronous with the pulse). This did not interfere with spectrophotometry. The arrangement of connections from the artery to cuvette provided for arresting of flow through the chamber, when desired, and bypassing it through a second channel to the artery. This permitted periodic trapping of samples at opposite phases of the respiratory cycle. In these particular experiments a tracheal cannula was employed for quickly changing from room air to 100% or 10% oxygen. Samples of blood were also removed for erythrocyte count and for independent spectrophotometric analysis of hemoglobin by the usual technique with the 1 cm. cuvette upon diluted, hemolyzed blood as HbO_2 , Hb (HbO_2 reduced by $\text{Na}_2\text{S}_2\text{O}_4$), and total pigment by conversion to MHbCN (cyanmethemoglobin).

Due to the presence of the anticoagulant dyestuff and lack of information concerning its level of maintenance in the blood stream, some uncertainty exists in the extrapolation of the true spectra from the data obtained in the turbid state. However, reliance may be placed upon a direct comparison of the extinction data obtained under varying conditions, and the agreement of results with those found upon hemolyzed blood, reported below. In the circulating blood, the concentration of pigment remained relatively constant (order of 5%) over a period of several hours. The percentage saturation was maintained at a level of 97 to 98%, assuming complete saturation under exposure to 100% oxygen. Samples trapped at "end expiration" showed a lower saturation (order of 2%) than corresponding samples (taken within several minutes), trapped at "end inspiration." The respiratory rate of the nembutalized animals was 10 to 12 per minute.

To avoid the use of Pontamine Fast Pink and turbid suspensions, thereby assuring full precision of spectrophotometric measurement, the following procedure was adopted. Small (6 to 15 ml. capacity) tonometers were employed as collection vessels. A solution containing 30 mg. of oxalate and 50 mg. saponin (to take care of approximately 4 ml. of blood, the size of the usual sample) was evenly air dried on the walls of the tonometer. The blood from the femoral artery of nembutalized dogs was delivered through a cannula and gum rubber connection, without contact with air, into the tonometers over clean mercury. The blood samples were collected in 3 to 4 spurts to synchronize with inspiration or expiration. By gentle shaking the blood was quickly hemolyzed. The hemolyzed sample was transferred to the 0.007 cm. cuvette, and spectrophotometry was begun within 2 to 3 minutes and completed within 6 minutes of the collection of the sample. The overflow of blood in the capillary entry and exit tubes effectively seal the chamber, so that oxygenation of the contained sample will not occur for periods of time up to 1 hour.

The rest of the sample of blood was transferred from the tonometer into a flat weighing dish. After exposure to air, portions were reread

spectrophotometrically in the 0.007 cm. cuvette with and without addition of $\text{Na}_2\text{S}_2\text{O}_4$. An aliquot was diluted and determined in the 1 cm. cuvette as HbO_2 , Hb, and MHbCN (see above). Excellent agreement was obtained in all analyses. No evidence of the presence of methemoglobin or pigments other than HbO_2 and Hb could be found. The absorption spectrum of the original sample, transferred directly from the tonometer to the special 0.007 cm. cuvette agreed with that expected theoretically for the approximate mixture of HbO_2 and Hb. The percentage saturation of the saponized arterial blood of 4 dogs was high: 98.2 to 98.7 at "end inspiration," 95.5 to 96.6 at "end expiration."

The Direct Spectrophotometric Determination of the Saturation of Hemoglobin in the Arterial Blood of Man.* D. L. DRABKIN, C. F. SCHMIDT, H. D. BRUNER, and H. H. PENNES (Depts. of Physiological Chemistry and Pharmacology, and the Harrison Dept. of Surgical Research, Univ. of Penna.). The oxygen saturation of the hemoglobin of arterial blood has been determined by direct spectrophotometry in 5 male subjects, 17 to 23 years of age, 4 of them normal and 1 a controlled diabetic. Four of the subjects were non-smokers, 1 had refrained from smoking for a period of 3 days before the experiment. The arterial blood was obtained under local anesthesia by the method of femoral puncture, using cut-down lumbar puncture needles (with stilus), gauge 19. With the stilus withdrawn a free, slow flow of blood was thus provided. The needle was allowed to remain in the artery for periods of approximately 1 hour, during which time periodic samples were drawn, without contact with air, into mercury filled, saponized and oxalated tonometers (as described in the preceding report). Respiratory data were taken during blood sampling.

The analytical procedures were carried out upon the saponized samples in the manner already described. The arterial saturation proved to be uniformly high in all the individuals—98 to 99.3%. The influence of the respiratory cycle upon the arterial saturation, found in nembutalized dogs, could not be demonstrated in unanesthetized man. It is concluded that the saturation of hemoglobin in the arterial blood of man is at least 2% higher than the previously accepted value of 95% based upon the indirect gasometric technique, and which corresponds to an arterial oxygen tension at sea level (read from the dissociation curve) of the order of 75 to 80 mm. Hg. Based upon the new value for saturation an arterial oxygen tension of the order of 95 mm. may be expected.

Normal Human Arterial Oxygen Tension.* JULIUS H. COMROE, JR. (Dept. of Pharmacology, Univ. of Penna.). No agreement exists in the literature in regard to normal oxygen tension in human arterial blood; figures as high as 99 and as low as 63 mm. Hg have been recorded and the generally accepted figure is 70 to 80 mm. Hg.

The present measurements have been made using the following technique: 15 cc. of arterial blood, collected anaerobically in a syringe and heparinized, are equilibrated with 20 to 40 c.mm. of alveolar air for 10 minutes at 37° C. During this period the blood and gas tensions equalize. The gas is then transferred to a Scholander microanalyzer and the oxygen percentage and tension determined. The error of the method,

* Work done under contract with the Office of Scientific Research and Development,

determined by analyses of equilibrated bloods of known gas tension is not more than 4.5 mm. Hg.

Thirteen subjects have been used: the arterial oxygen tensions varied from 83 to 100 mm. Hg and the average tension was 93 mm. Hg. These direct measurements indicate that the arterial oxygen tension is considerably higher than heretofore believed and cast serious doubt upon the accuracy of indirect calculations of O_2 tensions (using arterial pH and O_2 saturation as determined by the Van Slyke manometric method) especially when the tensions are in the 65 to 100 mm. range, corresponding to the flat portion of the dissociation curve for oxyhemoglobin.

Preliminary Studies on Respiratory Gas Mixing With Nitrogen as a Tracer Gas.* J. C. LILLY and T. F. ANDERSON (Johnson Foundation, Univ. of Penna.). A new instrument, the nitrogen meter, is described briefly. The device continuously and rapidly records the mol fraction of nitrogen in mixtures of respiratory gases and will accurately follow a change of composition occurring in 0.02 second. Records taken on oxygen equipment at altitude are presented. A method of determining the effective gas mixing volume of the human respiratory system is described. The subject breathes pure oxygen long enough to clear his lungs of nitrogen. Next he is connected to an electrical respiratory volume recorder and the nitrogen meter, and breathes air. The resulting nitrogen record in the expiratory phase shows an initial plateau of about 70 to 125 cc. due to expired air diluted with water vapor, a relatively rapidly falling portion of about 100 to 150 cc., and a final plateau for the rest of the expiration. The final plateau continues at the same nitrogen concentration found in a normal expiration even with a maximal expiration. From these records the total amount of nitrogen inspired and the total amount expired have been calculated; from the difference between these 2 amounts and the concentration shown on the plateau the lung volume available for mixing is calculated. The residual volume and maximum lung volume also have been determined from these records. The method has given consistent results on 5 subjects. Possible clinical research applications are mentioned.

The Diffusion Constant of the Lung. F. J. W. ROUGHTON (Fatigue Lab., Harvard Univ. and Dept. of Physiology, Coll. of Physicians and Surgeons, Columbia Univ.). On the Diffusion Theory of gas exchange in the lungs, the volume of O_2 (cc.) which can pass through the lung per minute = $\Delta pO_2 \times DO_2$ (1)

where ΔpO_2 is the average O_2 pressure difference (mm. Hg) between the alveolar air and the blood in the lung capillary. DO_2 is the diffusion constant of the whole lung to O_2 .

pO_2 is calculated from the alveolar pO_2 , the arterial pO_2 , and the mixed venous pO_2 by Bohr's method of graphic integration (*Skand. Arch. Physiol.*, 22, 261, 1909). DO_2 is obtained from $D CO$, the corresponding constant for CO as measured by Krogh's method (*J. Physiol.*, 49, 271, 1915). Its value, in different individuals, ranges from 25 to 50 at rest and from 30 to 70 at work. It is not affected by acclimatization to high altitudes (Harrop, *Proc. Soc. Exp. Biol. and Med.*, 19, 279, 1922).

* Work done under contract with the Office of Scientific Research and Development.

The applicability of equation (1) to work at low oxygen pressures furnishes the most crucial test of the Diffusion Theory; but unfortunately a survey of the literature (including especially the reports of the various physiologic expeditions to high altitudes) reveals only one pair of experiments in which all the necessary data are available. Asmussen and Chiodi (*Am. J. Physiol.*, 132, 426, 1941) in their work experiments at a simulated altitude of about 20,000 feet (breathing N_2 - O_2 mixtures) give the following figures: O_2 uptake per minute = 1600 cc., alveolar pO_2 = 45 mm., arterial pO_2 = 45 ± 2 mm., mixed venous pO_2 = 29 mm.

From these data I calculate that ΔpO_2 could not have exceeded 8 mm. at most; its exact value depends on knowing the arterial pO_2 precisely. For equation (1) to hold DO_2 must have been at least $1600 \div 8$, *i. e.*, 200—a value 3 times greater than the highest to be expected from Krogh's values for D CO. Either the Diffusion Theory is inadequate or the D CO determinations are much too low.

Haldane (*Physiol. Rev.*, 7, 363, 1927) has questioned the validity of the D CO method on the ground of incomplete mixing of CO in the alveoli. In recent data on the rate of CO uptake when breathing air containing low per cent CO (Forbes, Sargent and Roughton, unpublished) we have, however, found values in the same range as those of Krogh. Since our experiments lasted many minutes, incomplete lung mixture could hardly have been a factor.

Another possibility is the one I advanced 20 years ago (Ph.D. Thesis, Cambridge, 1925), namely, that the assumption of zero back pressure of CO in the blood during the D CO experiments may be in error owing to the slowness of combination of CO in the red cells. On this basis the values of D CO would be too low. My calculation distinctly favored this hypothesis, which has now been put on a more experimental basis by our comparisons (Forbes and Roughton, unpublished) of the rate of uptake of CO from air and from O_2 at rest and in hard work. (The rate of chemical reaction of CO with hemoglobin varies inversely as the O_2 pressure [Roughton, *Proc. Roy. Soc., B*, 115, 473, 1934] and hence the back pressure of CO in the blood should be much greater when breathing O_2 than when breathing air.) At rest the substitution of O_2 for air had no effect on the rate of CO uptake but in hard work it led to a 40% reduction in the initial rate of CO uptake. These data suggest that the values of D CO at rest are correct (the back pressure of CO being negligible), but in hard work require raising by a factor of the order of 20%. Even so, a large gap remains to be closed before the results of Asmussen and Chiodi can be explained on the Diffusion Theory. Further work on these lines is therefore planned.

BOOK REVIEWS AND NOTICES

NEW BOOKS

The Psychology of Women. A Psychoanalytic Interpretation. By HELENE DEUTSCH, M.D., Associate Psychiatrist, Massachusetts General Hospital Lecturer, Boston Psychoanalytic Institute. Foreword by STANLEY COBB, M.D., Bullard Professor of Neuropathology, Harvard University. Vol. 1. Pp. 399. New York: Grune & Stratton, 1944. Price, \$4.50.

The Genealogy of Gynecology. History of the Development of Gynecology Throughout the Ages, 2000 B.C.-1800 A.D. With excerpts from the many authors who have contributed to the various phases of the subject. By JAMES V. RICCI, A.B., M.D., Associate Clinical Professor of Gynecology and Obstetrics, New York Medical Coll.; Director of Gynecology of the City Hospital, New York; Associate Attending Gynecologist and Obstetrician, Flower and Fifth Avenue Hospitals, New York; Consultant in Gynecology and Obstetrics, Broad St. Hospital; Fellow of the New York Academy of Medicine. Pp. 578; 54 figs. Philadelphia: Blakiston, 1943. Price, \$8.50.

Tuberculosis of the Ear, Nose, and Throat: Including The Larynx, The Trachea, and The Bronchi. By MERVIN C. MYERSON, M.D. Dedication to DOCTOR HUBERT ARROWSMITH, Pioneer in Bronchoscopy and Laryngology. An outstanding worker in the field of tuberculosis. Pp. 291; 89 figs. Springfield, Ill.: Charles C Thomas, 1944. Price, \$5.50.

Manual of Human Protozoa. By RICHARD R. KUDO, D.Sc., Associate Professor of Zoology, Univ. of Illinois. Pp. 125; 29 figs. Springfield, Ill.: Charles C Thomas, 1944. Price, \$2.00.

Intercranial Arterial Aneurysms. By WALTER E. DANDY, Adjunct Professor of Surgery in Johns Hopkins University. Pp. 147; 55 figs.; 5 tables. Ithaca, N. Y.: Comstock Pub. Co., Cornell Univ., 1944. Price, \$2.50.

Aesculapius in Latin America. By ARISTIDES A. MOLL, PH.D., Secretary-Editor of the Pan-American Sanitary Bureau, Washington, D. C.; Consultant in Tropical Medicine to the Secretary of War; Honorary Professor of the Port-au-Prince Medical School; Former Editor of the Spanish Ed. of the *Journal of the American Medical Association*; Secretary (1933-1940) of the Pan-American Medical Association (Washington, D. C.); Secretary of the Tenth and Eleventh Pan-American Sanitary Conferences and the Second, Third and Fourth Pan-American Conferences of National Directors of Health; Decorated by the Governments of Chile, Columbia, Cuba, Ecuador and Haiti. Pp. 639. Numerous illus. Philadelphia and London: W. B. Saunders, 1944. Price, \$7.00.

Practical Malaria Control. A Handbook for Field Workers. By CARL E. M. GUNTHER, M.D., B.S., D.T.M. (SYDNEY), Field Medical Officer, Bulolo Gold Dredging Limited, Territory of New Guinea, at present with the Australian Medical Corps. Foreword by PROF. HARVEY SUTTON, O.B.E., M.D., F.R.A.C.P., B.Sc., D.P.H., F.R. SAN. I. Pp. 91. New York: Philosophical Library, 1944. Price, \$2.50.

Systematic Inorganic Chemistry. Of the Fifth-And-Sixth-Group Nonmetallic Elements. By DON M. YOST, Professor of Inorganic Chemistry, California Institute of Technology; and HORACE RUSSELL, JR., Instructor in Chemistry, California Institute of Technology. Dedication to WILLIAM C. BRAY, Able Scientist, Inspiring Teacher. Pp. 423; 78 figs. New York: Prentice-Hall, 1944. Price, \$4.60.

The Diet Therapy of Disease. A Handbook of Practical Nutrition. By LOUIS PELNER, M.D., Assistant Attending Physician, Long Island Hospital, Greenpoint Hospital, and Brooklyn Cancer Institute; Gastroscopist, Beth Moses Hospital; Lecturer, Post-Graduate Course in Gastro-enterology, under charge of Dr. S. A. Seley. Pp. 143. New York; Personnel Diet Service, 1944. Price, \$3.75.

Intravenous Anesthesia. By R. CHARLES ADAMS, M.D., C.M., M.S. (ANES.), Associate in Section on Anesthesiology, Mayo Clinic; Instructor in Anesthesiology, Mayo Foundation for Medical Education and Research, Graduate School Univ. of Minnesota, Rochester, Minn. Dedication to Dr. JOHN S. LUNDY, Friend and Teacher. Foreword by Dr. JOHN S. LUNDY. Pp. 663; 34 tables; 75 figs. New York and London: Paul B. Hoeber, 1944. Price, \$12.00.

One Hundred Years of American Psychiatry. Published for the American Psychiatric Association. By the following Contributors: HENRY ALDEN BUNKER, ALBERT DEUTSCH, J. K. HALL, SAMUEL W. HAMILTON, CLYDE KLUCKHOHN, WILLIAM MALAMUD, DOM THOMAS VERNER MOORE, WINFRED OVERHOLSER, RICHARD H. SHRYOCK, HENRY E. SIGERIST, EDWARD A. STRECKER, JOHN C. WHITEHORN, GREGORY ZILBOORG. Pp. 649; 35 illus. New York: Columbia Univ. Press, 1944. Price, \$6.00.

The Management of Neurosyphilis. By BERNHARD DATTFNER, M.D., JUR.D., Associate Clinical Professor of Neurology, New York Univ. Medical Coll. With the collaboration of EVAN W. THOMAS, M.D. Foreword by JOSEPH EARLE MOORE, M.D. Pp. 398; 40 figs.; charts, tables. New York: Grune & Stratton, 1944. Price, \$5.50.

The Treatment of Peptic Ulcer. Based Upon Ten Years' Experience at the New York Hospital. By GEORGE J. HEUER, M.D., Professor of Surgery of Cornell Univ. Medical Coll. and Surgeon-in-Chief of the New York Hospital. Assisted by CRANSTON HOLMAN, M.D., Assistant Professor of Clinical Surgery, Cornell Univ. Medical Coll., and WILLIAM A. COOPER, M.D., Assistant Professor of Clinical Surgery, Cornell Univ. Medical Coll. Pp. 118. Philadelphia: J. B. Lippincott, 1944. Price, \$3.00.

Technique in Trauma. Planned Timing in the Treatment of Wounds Including Burns. From the Montreal General Hospital and McGill Univ. By FRASER B. GURD, M.D., C.M., and F. DOUGLAS ACKMAN, M.D., C.M. In collaboration with JOHN W. GERRIE, M.D., C.M., EDWARD S. MILLS, M.D., C.M., JOSEPH E. PRITCHARD, M.D., FREDERICK SMITH, M.D. Preface by JOHN S. LOCKWOOD, M.D., Univ. of Pennsylvania; and Commentary by RALPH R. FITZGERALD, M.D., C.M., McGill Univ. Pp. 68; 17 figs.; 5 tables; 3 charts; 3 color plates. Philadelphia: J. B. Lippincott, 1944. Price, \$2.00.

Radiation and Climatic Therapy of Chronic Pulmonary Diseases. With Special Reference to Natural and Artificial Heliotherapy, X-ray Therapy, and Climatic Therapy of Chronic Pulmonary Diseases and All Forms of Tuberculosis. Edited by EDGAR MAYER, M.D., F.A.C.P., F.A.C.C.P., and 22 Collaborators. Pp. 393; 46 figs.; 15 tables. Baltimore: Williams & Wilkins, 1944. Price, \$5.00.

NEW EDITIONS

A Manual of Physical Therapy. Formerly published under the title "Physical Therapy for Nurses." By RICHARD KOVACS, M.D., Professor of Physical Therapy, New York Polyclinic Medical School and Hospital; Attending Physical Therapist, Manhattan State, Harlem Valley State, Columbus, and West Side Hospitals, New York. Third ed. Pp. 309; 29 tables; 118 figs.; 118 illus. Philadelphia: Lea & Febiger, 1944. Price, \$3.25.

Functional Disorders of the Foot. Their Diagnosis and Treatment. By FRANK D. DICKSON, M.D., F.A.C.S., Associate Professor of Clinical Surgery, Medical School, Univ. of Kansas; Orthopedic Surgeon, St. Luke's, Kansas City General, and Wheatley Hospitals, Kansas City, Mo.; Providence Hospital, Kansas City, Kan.; and REX L. DIVELEY, A.B., M.D., F.A.C.S., Colonel, Medical Corps, A.U.S.; Orthopedic Consultant, European Theater of Operations; Orthopedic Surgeon, St. Luke's Hospital, Kansas City, Kan. Second ed. Pp. 352; 202 figs. Philadelphia: J. B. Lippincott, 1944. Price, \$5.00.

Fundamentals of Psychiatry. By EDWARD A. STRECKER, M.D., Sc.D., F.A.C.P. Professor of Psychiatry and Chairman of the Department, Undergraduate School of Medicine, Univ. of Pennsylvania; Psychiatrist to the Pennsylvania Hospital; Attending Psychiatrist, Psychopathic Division, Philadelphia General Hospital; Consultant to the Bureau of Medicine and Surgery, U.S.N.; Consultant to the Secretary of War, A.A.F. Second ed. Pp. 219; 15 figs. Philadelphia, London and Montreal: J. B. Lippincott, 1944. Price, \$3.00.

BACTERIAL INFECTION. With Special Reference to Dental Practice. By J. L. T. APPLETON, B.S., D.D.S., Sc.D., Professor of Bacteriopathology and Dean, The Thomas W. Evans Museum and Dental Institute School of Dentistry, Univ. of Pennsylvania. Third ed. Pp. 498; 86 figs.; 5 color plates. Philadelphia: Lea & Febiger, 1944. Price, \$7.00.

The American Illustrated Medical Dictionary. By W. A. NEWMAN DORLAND, A.M., M.D., F.A.C.S., Lieut. Colonel, M.R.C., U.S.A.; Member of the Committee on Nomenclature and Classification of Diseases of the American Medical Association; Editor of "American Pocket Medical Dictionary." With the collaboration of E. C. L. MILLER, M.D., Medical College of Virginia. Twentieth ed. Pp. 1668; 885 illus.; 240 portraits. Philadelphia and London: W. B. Saunders, 1944. Price, plain—\$7.00; thumb-indexed—\$7.50.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

AUGUST, 1944

ORIGINAL ARTICLES

USE OF GELATIN SOLUTIONS IN THE TREATMENT OF HUMAN SHOCK*

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THE mechanism of shock is not completely understood. One of its recognized phenomena, however, is the reduction of the circulating plasma volume, due to either circulatory changes or to loss of plasma (local or into the tissues). In the latter case reduced plasma volume is associated with hemoconcentration.²³ Any attempt to rectify the decrease in plasma volume with or without hemoconcentration is considered rational in the treatment of shock.

Since crystalline solutions raise the plasma volume only temporarily^{16,24} and are thus ineffective, colloidal substances have to be employed; the most suitable being human plasma or blood. Since these are not available in unlimited quantities, plasma substitutes are being developed from macromolecular substances.

The first of these substances to be widely used was gum acacia^{4,14} which has been all but discarded because it is deposited in the liver.^{2,18} In recent years pectin,^{10,11,16,20} isinglass,^{29,30} and gelatin^{4,7,13,15} have been recommended as plasma substitutes. Within recent months several papers on the use of gelatin as a substitute for plasma in the treatment of experimental hemorrhagic and traumatic shock in dogs have appeared.^{8,17,25} The present study deals with the results of treatment of shock in humans by the administration of gelatin solutions. Gelatin is a mixture of various proteins, varying in type and molecular size in

* Supported by grant from the Upjohn Company, Kalamazoo, Mich.

different types of gelatins, depending upon source and preparation. It can be prepared as a non-toxic solution isotonic to plasma and somewhat more viscous than it. Experiments on rats, rabbits, and dogs carried out at the Upjohn Research Laboratories³¹ have demonstrated that the gelatin solution used in these studies is well tolerated without toxic effects.

Method and Material. The material of this study constitutes 52 patients in shock of differing degree and etiology. To evaluate the effect of treatment, the severity of shock was classified arbitrarily, because reliable uniform clinical criteria do not exist. The following rough method of estimation is not proposed as a classification of shock for general use; however, it appeared useful in evaluating the effect of another solution we used for the treatment of shock.²²

Mild. (1) Drop of systolic blood pressure not more than 30 mm. Hg as compared with the pre- or postshock level. (2) Increase in radial pulse rate.

Moderate. (1) Drop of systolic blood pressure more than 30 mm. Hg. (2) Decrease in volume of radial pulse with increase in rate. (3) Diaphoresis.

Severe. (1) Drop of systolic blood pressure more than 50 mm. Hg. (2) Barely palpable radial pulse ("thready"). (3) Cool clammy skin. (4) Restlessness.

Profound. (1) Blood pressure unobtainable. (2) Radial pulse unobtainable. (3) Rapid respiration. (4) Cold clammy skin. (5) Stupor. (6) Cyanosis.

Table 1 shows the type and degree of shock in the material examined.

In each shock patient, a record of the following clinical data was made: blood pressure, pulse, temperature, respiration and condition of the skin.

TABLE 1.—CLASSIFICATION OF THE 52 CASES OF SHOCK RECEIVING GELATIN ACCORDING TO ETIOLOGY AND SEVERITY

Type of shock	Degree of shock			
	Mild	Moderate	Severe	Profound
Postoperative	8	21	9	4
Traumatic	1	1	2	
Hemorrhagic	2	2	
Medical	2

Venous blood was obtained and placed in test tubes containing dried heparin.* A 5% solution of gelatin in normal saline was then intravenously administered, using the same needle with which the venous blood was drawn. The gelatin solution used in this study was prepared by the Upjohn Company, using a purified gelatin made from bone collagen. Calcium gelatinate prepared by electro dialysis was autoclaved, mixed with distilled water, sodium hydroxide, phenylmercuric borate and sodium chloride, passed through a sterilizing filter, and autoclaved again. The final product is a 0.9% sodium chloride solution containing approximately 5 gm. of gelatin in 100 ml. of solution. The pH is of physiologic range, the viscosity about 2 centipoises, and the oncotic pressure 70 mm. of mercury (\approx 5 mm.). The solution is preserved with 1:25,000 phenylmercuric borate. Total and non-protein nitrogen was determined on the final solution. Tests for sterility and for absence of pyrogens was carried out according to the U.S.P. XII.²⁷ In a period of 1½ or more hours 1000 cc. were usually given according to the severity of the shock. After infusion and 24 hours later, blood samples were drawn from the opposite arm and clinical data were checked.

In all blood samples the hemoglobin was measured with the photoelectric colorimeter.¹² The sedimentation rate was determined with the Wintrobe tube, the same tube being centrifuged after an hour for the hematocrit reading. The sedimentation rate was not corrected for change in red cell concentration.

* Provided by Roche-Organon, Inc. (Liquaemin), Nutley, N. J., and the Upjohn Company, Kalamazoo, Mich.

The density of the plasma as an index of the protein content was estimated with the falling drop apparatus of Barbour and Hamilton.³ Non-protein, protein, and albumin nitrogen were determined by Nesslerization.¹⁹ In the determination of the total protein nitrogen, as well as of the density of the plasma, the gelatin content has to be taken into consideration; further studies are planned to elucidate this relationship. The mean corpuscular hemoglobin concentration was calculated according to the following formula:²⁴

$$\frac{\text{Hemoglobin in gm. per 100 cc. of blood}}{\text{Volume of packed cells in cc. per 100 cc. of blood}} \times 100$$

The normal mean averages 35% and varies from 33 to 38%.

Where a statistical evaluation was made, the *t* value was determined,*⁶

* $t = x/s/n$.

x = Mean of difference between the determinations before and after gelatin administration.

s = Standard deviation.

We are indebted to Miss Elizabeth M. Adles for the statistical evaluation.

indicating the statistical significance of the difference between pre- and post-treatment results. Values of *t* of 2.5 or over are considered to indicate a significant difference.

Results. I. Incidence of Reactions. In none of the patients was there any evidence of pyrogenic or other untoward reaction to the gelatin administration. In none of them were chills, abrupt rise of temperature, or complaints of pain noted. A moderate rise of temperature (up to 2° F.) was occasionally seen, but could be explained by causes other than the gelatin administration (surgery, infections, etc.). No hemorrhagic tendencies were apparent. After the gelatin infusion, whole blood or plasma was repeatedly given without any complications. Some of the patients were under observation for over 1 month after gelatin administration and showed no sequelæ attributable to the administration.

II. Hemodilution. The mean of the hemoglobin, plasma density, total protein nitrogen, and hematocrit dropped markedly after the gelatin infusion and remained below control value for 24 hours (Table 2). The decrease was of statistical significance in all instances. The hemoglobin decreased slightly less and total protein nitrogen significantly less than the hematocrit.

TABLE 2.—INFLUENCE OF GELATIN ADMINISTRATION (IN 52 PATIENTS) ON THE BLOOD IN SHOCK

	Av. values prior to gelatin administration	Av. % change immediately after administration of gelatin	<i>t</i> value	Av. % change 24 hrs. after administration of gelatin	<i>t</i> value
Hematocrit	44%	-21.8	16.7	-15.8	9.9
Hemoglobin	13.7 gm./%	-17.9	14.6	-12.4	10.3
Protein nitrogen . .	6.7 gm./%	-9.8	7.0	-5.4	3.2
Plasma density . . .	6.97 gm./%	-12.2	14.1	-9.2	9.9
Non-protein nitrogen	31.7 mg./%	+4.5	1.6	+5.18	1.0

The decrease in the above factors varied in degree in different patients. Hematocrit, hemoglobin, and plasma density diminished in all patients immediately after the gelatin infusion, whereas the protein nitrogen increased in 6 cases. After 24 hours, there were increases in hematocrit, hemoglobin, and plasma density above the control level in 1 case each, and of the protein nitrogen in 11 cases. The albumin/

globulin ratio decreased from an average of 1.5 to 1.13 immediately after the infusion, the decrease being statistically significant; 24 hours later the average rose again to 1.42, however, without statistical significance (Table 3).

TABLE 3.—CHANGES IN SEDIMENTATION RATE, MEAN CORPUSCULAR HEMOGLOBIN CONCENTRATION, ALBUMIN/GLOBULIN RATIO, BLOOD PRESSURE, AND PULSE RATE AFTER ADMINISTRATION OF GELATIN TO PATIENTS IN SHOCK

	Av. values prior to gelatin administration	Av. change immediately after administration of gelatin	t value	Av. change 24 hrs. after administration of gelatin	t value
Sedimentation rate	29.2 mm./hr.	+25.6 mm.	14.2	+21.4 mm.	10.9
Mean corpuscular hemoglobin concentration	31.4%	+ 1.3%	1.9	+ 1.3%	2.6
Albumin/globulin ratio	1.5	- 0.37	4.1	- 0.08	0.5
Blood pressure:					
Systolic	77 mm. Hg	+42 mm. Hg	10.8	+45 mm. Hg	9.3
Diastolic	42 mm. Hg	+29 mm. Hg	8.6	+28 mm. Hg	5.8
Pulse	94.5/min.	0		+ 2.6	0.5

The non-protein nitrogen showed on the average an increase immediately and 24 hours later, but it was not statistically significant because of marked deviations in both directions.

III. Effect Upon Erythrocytes. The sedimentation rate which was, in the majority of cases, markedly elevated before treatment, consistently rose, the increase being statistically significant. The rise was maintained for 24 hours, and occasionally for 5 days. In general, in those cases in which the sedimentation rate had been markedly elevated to begin with, the rise after gelatin administration was proportionately less. This increase in the sedimentation rate was not influenced by dextrose, saline, blood, or plasma given following the gelatin.

The mean corpuscular hemoglobin concentration which, on an average, was originally below normal, rose consistently and was maintained for 24 hours, the increase at this time being of statistical significance.

TABLE 4.—THERAPEUTIC RESULTS FOLLOWING ADMINISTRATION OF GELATIN TO PATIENTS IN SHOCK

Degree of shock				
Mild	Moderate	Severe	Profound	
8	17	9	3	Gelatin solution alone relieved shock permanently
1	3	2	1	Shock relieved but blood also given for reasons other than shock (anemia, blood loss)
	2			Shock not relieved by gelatin but blood or plasma did relieve it
			1	Shock not relieved and patient expired
	1			Shock relieved only temporarily*
	1	2	1	Shock relieved but patient died of other causes

* This patient went into shock again the following day at which time a second infusion of 1000 cc. of gelatin relieved the shock permanently.

IV. Effect Upon Clinical Symptoms. The systolic and diastolic blood pressures, which were markedly reduced before treatment, rose

in all but 2 cases upon completion of the gelatin infusion and were maintained thereafter. The increase was statistically significant (Table 3). In 7 cases the blood pressure rose from zero to normal or near normal values. In patients with hypertension, the blood pressure was frequently restored to former hypertensive levels. Mathematical evaluations of the pulse changes were difficult because in 7 cases no radial pulse was present. In the rest of the cases which are listed in Table 3, no average change of the pulse rate was noted. Generally, an improvement in the character in the pulse was observed; changes in the skin from a cool clammy to a warm and dry condition were usually noted in those cases that responded.

Ordinarily, no consistent changes of temperature or respiration were encountered, excepting 1 case where the temperature rose 3° F. during the infusion; however, the underlying disease (abdominal carcinomatosis) may have been responsible for the rise.

V. Therapeutic Results. In the great majority of cases, one gelatin infusion relieved extreme as well as moderate shock, without any additional therapy (Table 4). In a few cases in whom gelatin had effectively relieved the shock, supplemental whole blood was administered for the treatment of an underlying anemia or profuse loss of blood. In 4 cases the gelatin did not relieve the shock, although in 2 patients blood or plasma infusion was successful (one associated with marked blood loss). In a third, (intestinal obstruction) both plasma and gelatin failed to prevent a fatal outcome; whereas a fourth went into shock again but was relieved by a second gelatin infusion. Four patients in whom the shock was relieved by gelatin, as seen from blood pressure response, died later from the following causes: burn toxemia in a diabetic, generalized peritonitis, bowel obstruction and ruptured esophageal varices.

VI. Repeated Administration. Gelatin administration was repeated in only 2 shock cases. One was a patient with surgical shock in whom a second liter of gelatin was necessary before shock was permanently relieved. A second case was that of a 50% burn of second degree; 2000 cc. of gelatin was given to treat the initial shock and then another 3000 cc. in the attempt to correct protein-deficiency. This patient, a diabetic, died on the 6th day, probably owing to toxemia.

Comment. The present study attempts to demonstrate the following points: 1. The administration of gelatin to patients in shock is a safe procedure. The only effect observed by us which has to be considered undesirable is the effect upon the erythrocytes. The increase of the sedimentation rate which is generally found upon injection of macromolecular substances was stressed by Ivy and his co-workers¹⁵ as an important disadvantage in the use of plasma substitutes after marked hemorrhage. If the number of erythrocytes is reduced to begin with, a further reduction of functioning erythrocytes by pseudo-agglutination (rouleau formation) is dangerous. The increased sedimentation rate is caused by the rouleau formation.

No evidence was found that in cases of shock without severe hemorrhage this increased sedimentation rate was of clinical significance. The increase in rate was not more marked than that found in acute infection, and if the sedimentation rate would be corrected for the reduced red cell count (due to hemodilution), the rise of the sedimentation rate would appear even less marked. No signs of peripheral venous thrombosis were noted. The increase of the mean corpuscular hemoglobin concentration is probably the result of a slight shrinkage of the red blood cells. Absence of low degree of antigenicity of gelatin has been demonstrated previously,^{26,28,33} as was also the fact that gelatin is not stored in tissues to a significant degree in contrast to other macromolecular substances.¹⁴

2. Gelatin solution is an effective hemodiluting agent. Part of its effect which is statistically significant is still encountered after 24 hours. The dilution of the red cells as judged from hematocrit and hemoglobin appears more marked than that of the plasma proteins. The values of both the total protein nitrogen and plasma density are influenced by the gelatin concentration in the plasma. The dilution of the plasma proteins is, therefore, more marked than can be interpreted from the determination of total protein nitrogen and plasma density. As gelatin influences the density of plasma to a different degree than the protein content, plasma density and protein nitrogen concentration run even less parallel than in other conditions. Since the protein of the gelatin is precipitated with the globulin fraction, a decrease of the albumin/globulin ratio may be anticipated. The non-protein nitrogen content of the gelatin may be responsible for the inconsistent increase of the plasma non-protein nitrogen; however, an exact evaluation is only possible if gelatin determinations are performed. For our present problem, the establishment of hemodilution suffices. The dilution of the plasma protein is not necessarily disadvantageous, since apparently not the plasma protein concentration but the total circulating plasma proteins are of significance.¹

Gelatin solution was an effective agent in the treatment of shock of every type and degree in which we used it, probably because it produced hemodilution. A comparison with plasma and whole blood was not attempted in this preliminary study. The failures, however, were few enough to warrant a favorable comparison. The number of cases is sufficient, we believe, to exclude spontaneous recovery as a reason for this favorable response.

One thousand cc. of gelatin in the concentration used seems sufficient because only in 1 case was a second dose required.

This paper suggests that gelatin solutions have the required qualities of a plasma substitute. Whether its nitrogen content has nutritional value after intravenous administration in shock, as in experimental animals,^{5,21,32} future investigations will have to decide. In view of the present shortage of plasma, gelatin may be a good substitute even if it should not be quite as effective as plasma itself.

Summary. Studies on 52 patients show that the administration of 1000 cc. of a 5% gelatin solution in normal saline was effective in the treatment of shock. It produced regularly a statistically significant hemodilution. No untoward effects were noted except an increase in the sedimentation rate, which, however, did not influence the clinical picture.

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INCREASES IN THE PLASMA VOLUME FOLLOWING THE ADMINISTRATION OF SODIUM SALTS*

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It has been demonstrated^{8,10-12,16} that the plasma volume does not remain fixed even with mild dehydration and will decrease in proportion to the severity of the dehydration. In normal subjects dehydration, induced by the administration of a low salt diet and ammonium chloride¹¹ or by the intravenous administration of 2 cc. of mercupurine,¹² is associated with a significant fall in the plasma volume. Under these circumstances, it appeared that the plasma volume was not well supported by the extracellular fluid and that the loss of water and salt, coincident to the diuresis, was associated with the fall in plasma volume.

If the plasma volume is reduced by relatively small decreases in the body water, it would appear likely that the reverse situation would also be true. The administration of sodium salts sufficient to produce a positive sodium balance, along with sufficient water, should increase the volume of the extracellular fluid and presumably the plasma volume as well. These studies were undertaken to evaluate the effect of ingestion of large amounts of sodium salts with water *ad lib.* on the plasma volume of normal subjects.

Methods. Fourteen hospital patients in good health at the time of the observations, without evidence of cardiovascular or renal disease and who had never had edema, were selected as normal subjects. Each subject had been on the routine hospital diet with fluid and salt *ad lib.* for several days before the observations began and was presumably in a state of normal hydration.

The subjects were studied in two groups: the first received sodium bicarbonate and the second group was given sodium chloride. On the day the observations were started, the subject was weighed in the rested, postabsorptive state on a beam balance accurate to 2 gm. Following this, he rested on a table, and blood samples were taken for the determination of the plasma volume,⁶ hematocrit,²¹ and serum protein concentration;² stasis was rigidly avoided in all instances. A measurement of the antecubital venous pressure¹³ was made during the blood sampling. In the first group, estimation of the hemoglobin concentration⁵ and red blood cell counts were made on the oxyalted blood samples taken for the hematocrit determination.

At the conclusion of the initial observations, the 6 subjects in Group I were given a liter bottle containing 25 gm. of sodium bicarbonate dissolved in 1000

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cc. of water. They were instructed to consume the contents of the bottle during the next 15 hours, taking 75 to 100 cc. per hour and to consume all the food on the diet trays. Each subject followed these instructions. All were permitted water *ad lib*. The following morning, the subject was again weighed and the initial observations were repeated. The same routine was again repeated, each subject consuming his usual diet and 25 gm. of sodium bicarbonate in 1000 cc. of water. The next morning after consuming 50 gm. of sodium bicarbonate in 48 hours in addition to his usual diet, the final observations were made.

The second group of 7 subjects were managed in exactly the same way except that 20 gm. of sodium chloride were given daily. The subjects were studied only after 48 hours on this régime and hemoglobin concentrations and red blood cell counts were not estimated.

One normal subject, R. C., the first to go on such a régime, received 40 gm. of sodium chloride daily for 2 days.

If the subject consumes his usual diet, significant changes in weight from one day to the next will reflect changes in the water content of the body. It can be assumed that changes in the weight of these subjects represents approximately the water held within the body. Certainly the error of such an assumption is of little significance in dealing with the relatively large and consistent changes in weight experienced by these subjects.

Twenty-two paired observations of the plasma volume repeated on successive mornings on control subjects in the rested, postabsorptive state, showed a mean variation from the initial value of $+0.68\%$, S.D. 2.8% , S.E. ± 0.61 . The mean percentage change in hematocrit was -0.79% , S.D. 2.63% , S.E. ± 0.56 . In 13 control cases the variation in serum protein concentration was -0.60% , S.D. 3.49% , S.E. ± 1.0 . From these control studies, it would appear that variations in plasma volume greater than 5% would occur only 7 times in 100 subjects pursuing their usual routine.

Results. The changes in the plasma volume, hematocrit, hemoglobin concentration, red blood cell count, serum protein concentration, venous pressure, and body weight for all the subjects are recorded in Table 1. The percentage change expresses the variation in the plasma volume more accurately than the actual change, since the plasma volume varies considerably with the size of the individual.

It will be noted in Table 1 that the body weight progressively increased during the 2-day period in the group receiving sodium bicarbonate, though the greatest change in weight occurred on the first day. In both groups there was a similar and fairly consistent increase in the body weight averaging 1.56 , ± 0.36 , or 2.3 , $\pm 0.17\%$, of the initial weight at the end of 2 days of sodium bicarbonate intake and 1.9 , ± 0.41 kg., or 3.1 , $\pm 0.73\%$ of the initial weight at the end of 2 days of sodium chloride intake. There was also a close similarity between the increase in the plasma volume noted in both groups. The average increase in the plasma volume after the 2-day sodium bicarbonate period was 400 ± 53.2 cc. or $14.4 \pm 1.54\%$ of the initial determination, while the group receiving sodium chloride had an average increase of 440 ± 35.5 cc. or $15.6 \pm 1.15\%$ of the initial determination.

In both groups the change in the hematocrit reading and in the concentration of serum protein failed to reflect quantitatively the change in the plasma volume as measured by the dye method. The relative increase in the plasma volume in nearly every instance was considerably greater than the relative decrease in the hematocrit or serum protein concentration as measured by the percentage change.

Thus in Group I at the end of the 2-day period, there was an average increase of 14.4% in the plasma volume, while the average decrease in the hematocrit was only 2.3% and in the serum protein concentration 6.9%. Similar findings were noted in Group II. Changes in the hemoglobin concentration or in the red blood cell count failed to show significant evidence of dilution and there was no significant change in the mean corpuscular volume of the red blood cells.

Discussion. From the results presented here, it is apparent that the addition to the diet of large amounts of sodium bicarbonate or sodium chloride results in significant increases in the plasma volume. Though sodium balance studies were not carried out in these subjects, others^{16,20} have reported significant retention of sodium and water following the administration of sodium bicarbonate or sodium chloride to normal subjects. It is, therefore, reasonable to suppose that the consistent increase in weight noted in these subjects was the result of the retention of sodium and water, and represents chiefly an increase in the extracellular fluid portion of the total body water.

Though there was considerable variation between the change in the plasma volume and the change in the body weight after the first day of sodium bicarbonate administration, both groups showed a fairly constant relationship between the change in the plasma volume and the change in body weight, at the end of 48 hours. Excluding Cases R. S. and V. V., the increase in plasma volume in the other 11 cases represented $23.5 \pm 6.8\%$ of the total gain in the body weight. In Cases R. S. and V. V. the increase in the plasma volume represented 92 and 84% of the gain in body weight. The slightly greater increases in plasma volume and in body weight noted in the cases receiving sodium chloride compared to the groups receiving sodium bicarbonate has little significance in this small series of cases. It should be noted, however, that more sodium was administered with sodium chloride than with sodium bicarbonate, and this alone might predispose to greater changes in body weight. Another factor impossible to evaluate in these cases is the diuretic effect of the alkali, which may in part explain the difference between the groups.

Since sodium retention produced in this manner is related to a significant increase in the plasma volume, it would seem that the plasma volume even of normal subjects cannot be assumed to be constant, but will vary with reasonably small changes in the water content of the body and presumably with the sodium balance of the individual. Krauel¹⁶ has demonstrated a fall in the plasma volume and body weight in normal subjects placed on a salt-poor diet. He also demonstrated that the addition of 10 or 20 gm. of sodium chloride produced an increase in the plasma volume and body weight. Decreases in the water content of the body produced by diuresis with a salt-poor diet and ammonium chloride¹¹ or by mercupurine¹² in normal subjects is associated with an average fall in the plasma volume of 14 and 16% of the initial determination. Thus it would appear that the plasma volume may be altered by relatively small changes in the body water of normal subjects to as much as 15% above or below the control

determinations. The fact that the plasma volume has been found to be relatively constant in normal subjects is no doubt due to the ability of the body to maintain a fairly constant sodium and water balance when variations in the intake of water and sodium are small.

The increase in the plasma volume following the administration of sodium salts with fluids *ad lib.* suggests that this mechanism might be useful in the restoration of the plasma volume after bleeding, in individuals who may be mildly dehydrated. In general the plasma volume is quickly restored to normal after small losses of blood,⁹ but after a blood loss of 15% of the total blood volume, the restoration of plasma volume is said to occur gradually.³ These studies suggest that the administration of large amounts of sodium salts as a preoperative measure will increase the plasma volume as well as predispose to a favorable water balance. This mechanism might also be of some benefit in operations in which a considerable blood loss could be anticipated, so that the plasma volume would be large at the beginning of the operation.

The failure of the hematocrit, hemoglobin concentration, and red blood cell count to change in proportion to the change in the plasma volume has been noted before^{4,11,12,15,18,19} in instances where the plasma volume has been reduced. It is apparent that under these circumstances, the cell elements in the antecubital vein from which the samples were drawn have not undergone the degree of dilution found by the direct determination of the plasma volume. This may be explained by suggestion of Ebert and Stead⁴ that there are shifts in the concentration of red blood cells between the smaller and the larger vessels with alterations in the plasma volume. They demonstrated⁴ that the cell plasma ratio for minute vessels is lower than in large arterics, veins or bleeding capillaries.

The failure of the serum proteins concentration to change in proportion to the alteration in the plasma volume has been noted before with decreases in the plasma volume.^{3,11,12,15,19} A similar situation is apparent in the cases reported here where the decrease in the serum protein concentration is not proportional to the increase in the plasma volume. This may be explained by the theory of Madden and Whipple¹⁴ that the serum proteins are in a state of dynamic equilibrium and may easily enter or leave the blood stream depending upon the stimulus so that the concentration remains relatively stable. These findings, along with those associated with a decrease in plasma volume, suggest that relatively small changes in the plasma volume in the normal subject will alter the amount of circulating protein in the plasma, so that the concentration of the serum protein in the plasma undergoes only small alterations.

The increase in the venous pressure in these cases may be explained either as a result of an increase in the local venous pressure, due to an increase in the tissue pressure, or as a result of an increase in the auricular pressure. Since the veins of the forearm are a series of collapsible tubes, the pressure in them is dependent upon the pressure of the surrounding tissues and the pressure in the right

auricle. An increase in the amount of extracellular fluid along the course of the vein might cause a rise in the tissue tone sufficient to cause partial obstruction of the vein and thus produce an elevation of the venous pressure. Ryder, Molle, and Ferris¹⁷ have indicated that the peripheral venous pressure is independent of the auricular pressure and is a function of the tissue pressure causing a collapse of the vein along its course to the heart. The variability in the rise in venous pressure noted in these cases suggests that in some instances the factor of local obstruction may play an important rôle. There is no experimental evidence in these cases that an increase in the auricular pressure did occur. However, with a diminution of the plasma volume, there was an associated decrease in the venous pressure and symptoms of a diminished blood flow suggesting a decrease in the auricular pressure.¹² It has been shown that the administration of intravenous fluids is associated with an increase in the cardiac output, especially when there was an increase in the peripheral venous pressure,¹ and it would seem likely that in these cases the increase in the plasma volume may be associated with an increase in the auricular pressure and with an increase in the cardiac output. In any event, the increase in the venous pressure noted in the antecubital vein would be associated with some increase in capillary stasis either local or generalized which would promote greater transudation of fluid from the capillaries into the interstitial tissues.

The considerable variation between the increase in plasma volume and increase in body weight noted after the first 24 hours on sodium bicarbonate compared to the more constant relationship in 48 hours suggests that the equilibrium between the plasma volume and extracellular fluid disturbed by the addition of salt and water had not been reestablished in 24 hours. It would seem reasonable to expect that as salt and water are absorbed from the gastro-intestinal tract the plasma volume is slightly increased. This gain in plasma volume may be at first quickly lost to the extracellular fluid spaces. With increases in the amount of fluid in the interstitial spaces the tissue pressure will be increased and will result in a decrease in the amount of fluid leaving the capillaries. At the same time, protein is added to the blood so that the osmotic pressure in the capillary does not significantly fall as a result of hemodilution, and the plasma volume may thus be maintained. If such a hypothesis be true, it should be expected that considerable variations would be found in normal subjects depending on the rate of absorption of water and salt, the rate of excretion, the volume of extracellular fluid, the tissue pressure, the capillary pressure, and the serum protein concentration.

Summary. 1. A significant increase in the plasma volume was noted in 14 subjects receiving large amounts of sodium chloride or sodium bicarbonate.

2. The increase in the plasma volume was accompanied by an increase in the venous pressure and the body weight, but was not accompanied by a proportional fall in the concentration of serum protein, hematocrit, hemoglobin concentration, or red blood cell count.

3. Six subjects receiving 50 gm. of sodium bicarbonate in 48 hours had a mean increase in plasma volume of $+400$ cc., ± 53.2 , or $14.4 \pm 1.54\%$, with mean increase of body weight of 1.56 , ± 0.358 kg., or $\pm 2.33 \pm 0.165\%$.

4. Seven subjects receiving 40 gm. of sodium chloride in 48 hours had a mean change in plasma volume of $+440 \pm 35.5$ cc., or $+15.6 \pm 1.15\%$, and a mean increase of body weight of 1.9 ± 0.41 kg., or $3.16 \pm 0.73\%$.

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ORIENTATION OF THE ARMY PSYCHIATRIST

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THE psychiatrist, probably more than the practitioner in any branch of medicine, is his own diagnostic and therapeutic instrument. Where the syphilologist has a laboratory, the radiologist an objective shadowgram of the particular bodily region which absorbs his interest, and even the internist a thermometer and the testimony of his auscultatory finger, the psychiatrist dealing with those functional disorders peculiar to his field must rely exclusively upon his understanding, his memory, and his judgment: understanding of human nature, of his patient's personality and of his particular problem; memory of other cases with their marked differences and subtle similarities; judgment to classify without doing his patient undue violence, to advise discreetly and to treat within the limits of anticipated benefit.

Experience has forged the general practitioner a yardstick which in a general way can be applied to medical disorders with positive diag-

nostic results. The index is flexible and must expand and contract within certain limits to include the atypical and the aberrant; but it is a poor physician who mistakes scarlet fever for a fractured femur and by no means an inept psychiatrist who mistakes a manic-depressive psychosis for schizophrenia. The internist could satisfactorily state whether or not a Martian was suffering from tuberculosis but the psychiatrist would be quite unable to decide whether he was psychotic, a genius, or an average extra-terrestrial specimen. In his own field the psychiatrist must get along without firm well-established clinical syndromes and must daily perform the paradoxical task of diagnosing and treating disorders of a perpetually unique nature. Psychiatric diagnosis is accordingly a subjective affair and the formal classification of any patient only a sort of makeshift which has no importance to the physician already familiar with the case, and only a limited value to his successor.

The only dichotomy between "Mind" and "Body" is happily an issue no longer. The competent internist, along with the specialist in the non-psychiatric branches of medicine, realize that it is impossible to treat a disease and ignore the patient; that taxes, marital disharmony and wayward children do have a bearing on John Doe's peptic ulcer. Yet for the proper diagnosis and management of our patients the new monism cannot be carried to absurd lengths. It is still fair to say that pneumonia has more connection with the pneumococcus than with the patient's distress over an early alopecia, and at the opposite extreme that the obsessive-compulsive states relate more to constitutional, environmental and conditioning factors than to microorganisms. The medically "ill person" is apt to be a more or less healthy "person" afflicted with a more or less serious "illness." In the psychiatric invalid the accent is reversed. His "person" is ill and his symptom manifestations are but the disruptive reverberation of this central canker. Try as we will we may be unable to find that an attack of chickenpox has had any relationship to our patient's personality, but we are not obliged to believe that a psychoneurosis has its prodromal, clinical and convalescent stages, leaving the same old "normal self" with a few added scars.

Measles and carcinoma of the breast bear more resemblance than measles and schizophrenia, in the same sense that one recognizes oranges and apples as more akin than oranges and justice. To approach psychiatric disorders with a "yardstick" of symptoms and signs, to hope that a "Wassermann test" for hebephrenia will eventually come out of our research laboratories, to visualize an exogenous disease process descending upon the organism in the way that typhoid fever invades its victim, is to plunge unprofitably against a permanent and sterile impasse. One does not attempt to adjust a mine-workers' strike with a kit of mechanic's tools nor does one grind the valves of an internal combustion engine with Emerson's Essays.

The medically oriented physician is told by the psychiatrist that he must consider the intangible elements in his cases, yet he may not be informed that his familiar tools, his diagnostic and therapeutic tech-

niques and perhaps most importantly of all his very habits of thought must be discarded and a radically divergent approach adopted. Psychiatry is not an exact science, nor is politics, nor philosophy. What does one weigh? What does one measure? Modern clinical medicine, although few would include it in the relatively exact disciplines of physics and chemistry and certainly not in the completely "scientific" field of mathematics, still employs genuinely scientific techniques which have resulted in the brilliant advances of the past few hundred years. Psychiatry, when dealing with those disorders preëminently its own, has signally failed whenever it has attempted to employ the same approach. Psychiatry's spiritual father is Aeschylus and not Hippocrates, and its practitioners have more to learn from Phidias, Shakespeare, El Greco and Milton than from Sir William Osler.

Therapeutics, *per se*, is intimately related to the practitioner's understanding of his individual patient and in the reversible disorder, productive or ineffective in direct proportion to the physician's grasp. The psychiatrist must, therefore, be at all times keenly aware of his own "tare" which will inevitably and radically vary, depending on the type of practice he is doing and upon the circumstances of his own existence both environmental and subjective. His experience, actual and vicarious, must be of an extent and diversity to permit him a common ground with every patient who comes under his care. As this common ground narrows, his ability to diagnose and to treat recedes and may eventually reach a hypothetical point of non-existence. It is a dim realization of the validity of this by the relative and lay friend that leads him so often to insist that he "knows" the patient "inside out" and so can do far more therapeutically than the psychiatrist. The basic premise is sound but the application is in error since this "knowledge" is usually more of the patient's effect upon him than of the patient. Furthermore, the ability to use even what objective knowledge exists is stultified by his personal ties.

It is the psychiatrist's constant effort to understand rather than to sympathize, to be objective rather than partisan, and at the same time to know his own prejudices, aims and fidelities and when they minimize one facet of his patient's personality and exaggerate another to make the necessary correction in his conclusions. A form of identification takes place with the sufferer, a projection into his being. He strives to react with another's instincts, feel with his emotions, think with his mind, all in an attempt to strike closer to the knowable truth concerning him. Not the metric truth of cubits in his stature, not the subjective truth of chiming music in his voice, but rather the transcendental truth of Who He Is.

Remote as these comments may seem from the practice of Army psychiatry I shall endeavor to demonstrate their relationship.

The civilian psychiatrist will usually be found in institutional work, penal consultation, private practice or the psychiatric out-patient clinic of a University or Foundation. In the State Institution the patient census is made up of individuals deriving from a relatively narrow geographic area. In a general way their economic situation is

similar. By and large they are all psychotic. In practically every instance their illness has been of sufficient severity to attract social notice culminating in their commitment.

In penal work individuals coming to the psychiatrist's attention are even more rigidly "selected." All, if not actual criminals, have at least been accused and convicted of anti-social acts. All face an essentially identical environmental situation: enforced confinement and social stigma.

The private psychiatrist, perhaps most of all, sees a sharply differentiated group of patients. His work will be done within certain economic brackets, the majority of his cases will share with each other either an awareness of their illness and a desire for help, or will have families who recognize these issues more or less completely. He will continue to treat only those who feel they are profiting by his assistance or whose families hold this opinion.

The physician working in a private sanitarium, in an out-patient clinic, in a teaching Institute will in turn find that his practice has a certain year in, year out uniformity that in itself facilitates the discharge of his responsibilities.

In general, then, one may say that the civilian psychiatrist in whatever field he may be working, deals with a highly *selective* group of patients who share with one another many important similarities and who either recognize the fact of their illness or have others (the family or society) who do so for them. The psychiatrist can in consequence approach a case with a background of familiarity, the very existence of which he may not recognize. He is usually aware of the mores which have impinged upon his patient because they have also influenced the physician. He knows automatically from the patient's address in what climatic conditions he has been living. It is not improbable that he may know the patient's employer or the reputation of the business house of which he happens to be the head. His dress tells as much about his personality as it does about his pocketbook.

In military practice the geographic, economic and social background of the patients is heterogeneous to a degree that has no civilian counterpart. Every State in the Union is represented, every financial situation, every intellectual endowment, every cultural level. The millionaire wears the same shade of olive drab as the pauper. The genius salutes with the same gesture as the mental defective. The Maine woodsman inflects his "Sir" in the same fashion as the California hotel manager. He comes under the observation of the medical officer for one reason only, failure to be a satisfactory soldier. He may, of course, be ill and often is, but the line officer and the first sergeant are not functioning as health advisers. They naturally and correctly evaluate the enlisted man as to his military possibilities. How able a salesman may be, how satisfactorily a coal miner has met his civilian problems, what magnificent books an author has written, are no longer pertinent. Can he fight? Is he of any use in one of the services of supply? Men who are not "good soldiers" include a great many human types with whom the psychiatrist has had no previous contact and yet

in a great many instances it is just these men that, in course of time, he is asked to evaluate.

The civilian psychiatrist has *ipso facto evidence of the patient's illness* in the average professional situation, for otherwise no provision would have been made for his examination. To him, "What illness afflicts this individual?" is a rather different question than "Does this patient have any type of disorder?" Only in the field of industrial medicine where compensation and liability necessarily bulk large is he asked the second question as often as in the Army.

To the civilian population of the United States and correspondingly to its medical practitioners Peace is thoroughly comprehensible; War, strange, European, and largely inexplicable. It is far easier to understand the plumbing business, the stock market, library schools and Ringling Bros. Circus than it is close order drill. Although Americans have fought considerably more than the continental average of a war a generation they have remained singularly untouched by militarism in any of its manifestations, concrete or ideologic. Even such a simple military prerequisite as conscription had to be elaborately disguised and fitted with a euphemistic title that appealed to peace-time fetishes. The deep-sea diver, and the lumberjack talked a language in 1941 far more comprehensible to the psychiatrist than can be spoken by any sergeant to his recently commissioned medical officer. The psychiatrist newly in uniform not only has no understanding of the *War Situation* in which his patients find themselves, but, since his duties confine him to the purlieu of the hospital, has little means of finding out. What do the men talk about when no officers are present? What is the actual effect of disciplinary action on group morale? Just how "tough" is a sergeant? What does Private John Doe really think about the war, about giving up his job, about relinquishing what he has always thought was personal control of his own destiny? What is the "average" soldier like? These and many other questions he is obliged to ask himself, for it is only through his ability to answer them accurately that he can fulfill his professional function.

A no less challenging task before the psychiatrist lies in familiarizing himself with the *Aims of the Army*. What constitutes disability in the psychiatric field? What is the minimum standard of the individual soldier's performance which makes him an asset rather than a liability to the armed forces? The answers to these and kindred queries are not as simple as might at first appear. Man has sought throughout the ages for codification, believing perhaps naively and perhaps not, that through carefully worded regulations and the establishment of standardized procedures, recurrent situations could be dealt with in a uniform and just manner. Moses' Ten Commandments, the Roman Law and the Napoleonic Code were such attempts. Army regulations and the Articles of War are others. Admirable as these guides are, they do not, nor can any such body of regulations hope to avoid interpretation or the inescapable fact that they will be administered by human beings in connection with human situations. It is possible so to interpret AR 615-360, Sect. VIII that any individual in

whom signs of viability are present and who is able to make a purposive movement such as lifting an arm must "by regulation" be retained in the Army, even though he be an overt homosexual, a morphine addict and have a mental age of 3 years. It is also possible so to interpret this regulation that an infantryman afflicted with a degree of native awkwardness greater than that shown by his fellows but with the sterling qualities of a Sergeant York must "by regulation" be dismissed from the service. The psychiatrist must learn where along this interpretive scale are the limits of actual practice at his particular post and in his particular organization, for although the regulations throughout the Army are uniform, it is no secret that a "Section VIII Discharge" may be "easier" under Colonel B. in Maine than under Colonel A. in Texas.

Education constitutes the last category for discussion. The civilian psychiatrist in every professional situation in which he may find himself, with the exception of a certain type of forensic practice, is dealing either with other psychiatrists (the Psychiatric Institute's seminar; the State Hospital conference) or with medical practitioners who have sought his advice and who accordingly are quite ready to accept his judgment and interpretation. In the military field the final decision regarding his cases frequently rests with a board of medical officers entirely untrained in psychiatry, whose efforts to fit the needs of an individual problem to the printed regulations may not invariably be in accord with Army aims. With the authority of such a board to pass on what standard of performance is requisite in the individual soldier for military service there can, of course, be no argument, but it is both the privilege and the duty of the psychiatrist to make certain that the members of the board are fully informed of his patient's status and of the "life history" of the disorder with which he is afflicted. He is handicapped by having no roentgenograms with which to demonstrate the disability, no objective physical signs which all can test for themselves, so that there is no particular occasion for surprise when a non-psychiatrically oriented board hesitates over the discharge of a psychoneurotic of perfect physique and superior intelligence.

Once the psychiatrist's standards are brought into conformity with Army Aims, once he has become "psychiatrist to the American soldier" and can interpret and understand the Tennessee mountaineer equally with the Detroit shop worker and the Vermont farmer, once he has learned to differentiate between an illness and a case of guard-house boredom, once he knows what the war situation means, first to himself and then to his patient both environmentally and subjectively, he is in a position to help his professional confrères to an appropriate course in handling his patient's problem.

The following cases are offered for consideration, illustrating in a concrete way, it is hoped, certain of the issues raised above. The first is close to being a man from Mars and demonstrates the difficulty of psychiatric evaluation when the racial and cultural background of a patient is unfamiliar to the examiner. It is problematic whether any

but a New Englander could thoroughly understand the second man and doubtful that either he or the third case would have come to the attention of a civilian psychiatrist. The traditions, personalities, symptom-complexes, motivations and maladjustments of all are unique and their respective diagnoses distinctly subjective and legitimately open to question. None had any objective physical illness, none showed abnormality on laboratory studies and none was functioning in a healthy fashion.

CASE 1. A.B. was a Japanese prisoner of war admitted to the Hospital after 10 months in the Enemy Alien Stockade. A number of his fellows insisted he was insane, while others declared he had only incurred the dislike of a certain clique among the prisoners by his independent ways. Officers in charge of the Stockade reported him as being uncoöperative and resistive to discipline. On several occasions he had been seen by Army personnel openly masturbating and once was said to have completed the procedure in the midst of several waiting soldiers, finally turning to them and blandly asking their business with him. An opinion regarding his mental health was desired.

The patient was a short, wiry Japanese of 41, pleasant in manner and coöperative to hospital regulations. He preferred to remain bare-footed and when seated in a chair would draw up his knees until his feet rested against his thighs. He moved with the quickness and agility of an acrobat, and his gait invariably held something of a swagger, borne out by the habitual expression of tolerant superiority and amused indulgence with which he spoke to the examiner. The most striking thing in his appearance was a full black beard which he wore with obvious pride. His grasp of English was rudimentary and it was with the utmost difficulty that any verbal interchange could be effected.

He had been born in Japan, November 1, 1902, the third of 5 children. One sister had died at 10 of influenza. He had heard nothing of the remaining siblings since their immigration to Brazil 10 years previously. His father, a farmer and a keeper of the Shinto shrine in his village, had died at 65 of heart disease and his mother at 61 of "kidney trouble." Familial diseases were denied. The patient disclaimed neurotic traits, illnesses, serious injuries and operations, declaring, "Since I am born I never been sick. Always strong. Healthy family." It was apparent that he took much satisfaction in his robustness. He had started school at 7 and had stopped at 16 completing the 8th form in a Japanese public school. He claimed to have always had a high scholastic average and to have gotten along well with his contemporaries and instructors. He held class offices in school and was active in athletics, particularly track and swimming. He was not interested in furthering his education beyond the minimum required by law, having made up his mind at an early age to travel.

For 4 years after leaving school he worked on his father's farm, a property of 50 acres, said to be an average size for his country. At 20 he moved to Tokio where he lived with his step-brother, a wholesale merchant in an especially fine grade of silk woven in the patient's own village. During the days he assisted in his step-brother's store and at night attended school where he learned his first English. At 22 he came to the United States and lived in and about New York City until December 1941 when he was taken into custody as an Enemy Alien. In the United States he operated concessions at amusement resorts and claimed to have owned several wholesale and retail businesses dealing in Japanese merchandise. His average income was between \$40 and \$50 a week. He drank and smoked in moderation but denied the use of drugs. He stated he had resorted to prostitutes once or twice a month until the age of 30, but with the subsequent decrease in his sexual urges had felt little interest in coitus. He had never been married or engaged, declaring there was "too much trouble" associated with the marital state. He gave his religion as Shinto and stated that he observed its tenets faithfully.

The patient stated that movies, reading, and watching athletic events were his chief interests and spoke of going occasionally to Coney Island or Long Beach to swim. Some 10 years previously he had abruptly severed all social contacts except with his immediate relatives declaring: "I like peaceful living, quiet. Thinking. Study time. So I didn't make friends. I know many people but not close you understand. All simple." He denied that anything happened at this time to influence his decision. "Just my own desire you know." He further stated that 3 years previously he had severed all correspondence with a step-brother living in Stamford, Conn., by common consent, since they did not want to have "trouble." No clarification of what constituted "trouble" was possible except the patient's puzzling idea that all human contacts in the United States were dangerous because there was no "righteousness" and too much "competition." He had no hobbies, belonged to no societies or clubs and cultivated no cultural interests. He had never been arrested.

One of the officers from the Stockade reported that the patient had been difficult to manage from the time of his arrival and had never considered himself bound either by military discipline or the regulations set up by the Japanese internees. He bullied his tent mates and spent much of his time striding about the area smoking a pipe and swinging a cane. The other prisoners were said to avoid him as much as possible. Many of them were afraid of him and some regarded him as mentally unbalanced. At mess call he would frequently continue his promenade and, after the other men had been fed, demand something to eat for himself. Gossip among the Japanese was to the effect that he had at one time been a patient in a mental hospital in New York or Massachusetts. They also believed he had adopted his present name several years previously when he became estranged from his relatives because of his irresponsible conduct, shiftless ways and frequent intoxication.

In hospital most of his answers to questions were circumstantial and seemingly tangential. In reply to almost every query he brought in some mention of his religion and philosophy. He flatly denied open masturbation as reported by the officers, stated he got along well with the other men and denied that he had ever been in a mental institution. He did not regard the Japanese spokesman at the Stockade as a suitable choice since he was a Christian convert and a missionary, and accordingly could not properly represent those of his race who were of other faiths. He admitted that he did not consider himself bound by any decisions made for the group by this leader. He professed to be on excellent terms with what relatives were living in the United States and declared he never became drunk oftener than once a year and then only for a short period.

He was eager to point out the defects of Western civilization and to praise Japan's cultural advantages. He talked at length about Shintoism and its basic concept of Righteousness, from which stem Humanity, Freedom and Liberty. In some way not clear to the examiner he justified his friendlessness and isolation on the absence of a patriarchal social organization in the United States. The natural order, he maintained, was for the family and all society to be hierarchial, with the male dominant, the female under his jurisdiction and children at the lowest stage. This was proved, he contended, by the fact that the sun is male, the moon female and the stars immature children. Some 10 years ago he awakened to the dangers and potential "troubles" of friendship and subsequently isolated himself as completely as possible from his fellows, maintaining only "simple" (casual?) relations with them. He declared with a great deal of pride that he was a "student," and had thoroughly examined Western civilization with especial reference to its religion and its politics. He liked "a quiet life" in which his meditations were not disturbed and became almost ecstatic in describing its merits. He regarded his hospitalization as a "double cross" initiated by a small Japanese clique among the prisoners who did not regard him highly and who had succeeded in duping the Army personnel into a belief that he was "sick." He was certain there was no rational motive for this, declaring it was only because these men were "nervous"

(insane). The patient's sensorium was entirely clear, his mood was undisturbed, it was not possible to elicit hallucinations and his intelligence appeared to be adequate although probably no more than dull normal.

Cultural and racial differences, the language barrier and the effect of war attitudes on the patient's candor raised insoluble difficulties in formulating his disorder. Was he only an eccentric and lonely man of modest endowment reacting to a hostile and incomprehensible physical and spiritual environment by a schizoid retreat and the glorification of a self-created philosophy and half-fabricated religion which he identified with his home land? Was he a wastrel and an outcast, a rowdy vagrant? Was he, in reality, a schizophrenic whose overt symptomatology appeared 10 years previously when he retreated from society, fell out with his relatives, and became economically ineffectual? Was he, in his present situation, dramatically manifesting further dilapidation in conduct by his open masturbation? It was readily ascertained that he did not have syphilis, that he was not suffering from pulmonary tuberculosis, that he was not a victim of diabetes. No finely calibrated scale was at hand to determine whether or not he was insane.

CASE 2. C.D. was a native of Vermont who had been in the Army for 5 months. He was referred to the Hospital because of stomach trouble which had been particularly troublesome within the past year and which he stated was relieved at times by taking food and at times by passing flatus. He was originally admitted on a medical ward. Gastric analysis was normal and he displayed no secondary anemia. A barium enema showed no evidence of colitis or other pathology in the large bowel and his feces were negative for occult blood. Cysts and pre-cysts of *Endamaba coli* were repeatedly found but were not thought to have an etiologic bearing on his complaint. Twelve days after admission he was seen by a psychiatric consultant. He spoke of being "nervous" for a long time, but was unable to date the onset more accurately. He stated he was easily excited, was often "shaky," suffered from palpitation and described prickling sensations in his arms and "funny feelings all over" for which he could not account. He admitted that he was "kind of depressed at times" and that he seemed constantly on the verge of weeping. He had been unable to sleep well during his period of military service because of the noise from card players and from intoxicated soldiers coming into the barracks late at night. He was transferred to a psychiatric ward the same day.

The patient was 37 years of age, of medium build and of a courteous and retiring manner. Throughout his subsequent hospitalization he spent much of his time alone in his room, at times reading and at times in idleness. He volunteered no complaints, rarely spoke to the other patients and showed no interest in the activities of the ward. His facial expression was sober rather than depressed, he showed no signs of retardation and his apparent preoccupation was never of a degree to impair his awareness of his surroundings. He readily carried out whatever housekeeping tasks were assigned him and replied pertinently and without hesitation to questions addressed him.

He had been born in Vermont, November 2, 1906, the third of 4 children. One brother died at 36 after 25 years in a mental institution probably for an epileptic psychosis. The 2 remaining brothers were living and well. His father, although still alive at 72 was in delicate health and his 70 year old mother suffered from "nervous trouble." Familial diseases were denied except for 2 instances of fatal tuberculosis. He was uninformed regarding his birth and early development but stated that temper tantrums had been common in his childhood and that he had never outgrown the habit of biting his nails. Other neurotic traits were disclaimed. He had suffered from all the minor exanthemata and at 10 had undergone an attack of scarlet fever without apparent residuals. A tonsil and adenoidectomy was performed at 27 and a herniotomy and appendectomy at 33. At 21 or 22 he had acquired gonorrhea which was followed by an arthritic involvement of the left knee. This continued to cause him pain after any unusual exercise. Other serious illnesses and operations as well as injuries of significance were denied.

He had completed public high school at 18 with a scholastic average of

"C." There had been occasional truancy, but in general his deportment had been good. He had gotten along with both instructors and classmates without trouble, but had mixed little with the other students and had never been a popular boy. He had participated in none of the extra-curricular school activities, belonged to no societies, taken no part in athletics and had never held a class office. Although his family would not have objected had he wished to enter college, he had shown no interest in furthering his education.

After leaving high school he worked for the following 4 years as a marble cutter, fashioning cemetery stones. For a time his salary was \$70 a week. At 21 he and 3 companions were making a purchase of some beer from the local bootlegger when an argument arose over their having been short-changed. One of the patient's companions struck the bootlegger with his fist, discolored his eye. The man brought charges against all 4 and the patient and 2 of his companions were sentenced to 9 to 12 months in the penitentiary. The patient was released after 8 months, immediately gave up both alcohol and tobacco to which he never subsequently resorted and changed his employment from stone cutter to handy man in the kitchen of a Fine Arts College in his home town. He remained for the following 15 years in the same employment at a salary of \$25 a week. After several years he was made assistant cook. He would visit at home several times a week and would occasionally stay overnight with his family, but actually made his home at the College where he lived with 4 to 6 other employees, pastry and meat cooks, dish washers and kitchen men. Throughout this period he never went out socially with any of his fellow workers, never participated in the activities of the common room which they all shared, and consistently kept to himself.

His alcoholic indulgences, which for a time reached a maximum of one pint of spirits in the 24 hour period, were confined to his young manhood, the patient drinking nothing before he was 18 and nothing after his release from prison at 22. Tobacco was abruptly discontinued at the same time. "My stomach and nerves couldn't stand it," he explained.

The patient's family were Congregational by faith and quite devout in their observances. The patient had never been interested in formal religious issues but considered himself a Christian man. He had never married or been engaged and admitted that even casual social contacts with members of the opposite sex were infrequent. He had never resorted to prostitutes, had never fallen in love and could even recall the approximate number of sexual contacts in which he had participated during his lifetime. Homosexual experiences were denied. Concerning masturbation he stated that "of course it would injure your health and run you down." He felt it "couldn't help but weaken the mind." Although evasively denying that he had observed any such harmful effects upon himself and disclaiming any fears that he might go insane as the result of the practice, it was evident that he had given the matter considerable thought.

His amusements had consisted of attendance at the movies 2 or 3 times a week, of hunting and fishing, of reading the newspapers and of listening to the radio. His hunting was done alone because "there wasn't so much noise," he rarely "bothered" to go with any one to the theater and it was naturally more convenient to read and to listen to the radio in the privacy of his room. He had no hobbies and no cultural interests. On his visits at home he almost never came in contact with anyone but his immediate relatives since they "didn't go out much or have people in." He had been arrested but twice: once at the age of 20 for drunkenness and again at 21 for disturbing the peace. It was following conviction for this offense that he spent 8 months in the penitentiary. In the Army he had been subjected to no disciplinary action and had never before been hospitalized. He had reported on sick calls some 4 or 5 times in all, invariably complaining of his stomach.

The patient was unable accurately to fix the date of onset for his complaints of "stomach trouble," dyspnea, precordial distress, tension, epigastric burning and "nervousness" but stated they first became noticeable in early manhood. In search of relief he gave up both tobacco and alcohol at 22 but continued to

he intermittently troubled in the following years. In 1942 his symptoms grew so annoying that he consulted a physician who, after a thorough examination, declared they were the result of "nervousness" rather than of any organic pathology. Military service, so greatly out of keeping with his customary life pattern, aggravated his complaints. He was unusually distressed by the noise and bustle of camp life, the propinquity of other soldiers and the rapid pace of events. He became depressed and episodes of tearfulness were common. His outstanding complaint on admission to hospital was of gastric distress, and initial examination procedures were conducted on an appropriate medical ward. They failed in every instance to demonstrate an objective basis for his trouble. The patient displayed no disorder of speech, no projectional delusions and no hallucinations. His sensorium was normal and his basal intellectual faculties intact and adequate.

Could the abrupt relinquishment of a profitable trade, the apparent contentment in a poorly remunerated, semi-domestic job, the sudden renouncement of the sins of tobacco and alcohol have been the profound reaction of a conscientious and penitent youngster to an adolescent misdemeanor which society had punished by a harsh penitentiary sentence? Were the inflexible rigidity of his past life, the paucity of his interests, the habitual seclusiveness of his existence but a literal application of New England traditionalism, personal restraint, and conventionality? Was he a neurotically insecure, poorly adjusted and distinctly schizoid personality hiding from the stresses of human contact in the basement of a College dormitory, perverting his instincts, disrupting his personality and sinking continually deeper into hypochondriacal dilapidation? Had his native store of initiative, of energy, of interest, burned itself out before he was 22, leaving him an emotionally empty and purposeless derelict who maintained the illusion of human, although somewhat eccentric behavior until he was taken out of his habit-bastioned environment and thrown into the parlous uncertainties of an Army camp? Was he a Saint, a New Englander, a Psychoneurotic, a Schizophrenic, or was he C. D. the unique creation of an endlessly inventive Providence?

CASE 3. E.F. was born in New York City, and first entered a military hospital after 9 months of service. The psychiatric out-patient report authorizing his admission read as follows: "Profound depression. Marked feelings of depersonalization. A great deal of content is schizoid. Admit to closed ward." His commanding officer stated that he had found the patient intelligent but unadaptable, that his only interest was in textiles, and that he was "completely useless" in his present assignment in the Infantry. Every effort made by his organization to effect his transfer to the Quartermaster Corps had been unsuccessful and it had been decided to refer him to the Hospital in the hope that he could be reclassified. The patient insisted that in his attempt to persuade the medical officer of the need for his transfer he had overstepped himself and convinced him rather that he was mentally ill.

The patient was a man of large but unathletic physique, coöperative, suave, and volubly eager to make clear his situation and to correct the physicians' erroneous notion that he was psychotic. He mixed little with the other patients and spent much of his time reading and carrying on a voluminous correspondence. He immediately began to ask for unusual privileges, particularly the use of the telephone, and at no time let it be thought that he considered himself one of the ward patients. He was on terms of easy condescension with the attendants, showed a polite reserve toward the nurses and was respectful but faintly impatient with the medical officers. He collaborated with them on his "case," exchanged suggestions, and permitted himself no doubts that all concerned were of one mind as to the proper thing to be done. Ascertaining on his first day in hospital that all outgoing mail was read by the doctor before it was posted, he instituted a campaign which made up in volume for what it lacked in subtlety. He discussed his situation *in extenso* with a half dozen correspondents and when no more remained, began to cycle again, interminably repeating himself even as to the phraseology in his numerous letters. His speech was rapid, emotionally surcharged and for the most part overpower-

ingly plausible, an odd, elliptical, short-hand utterance with many elisions and apparent indirections which he was, nevertheless, always able to clarify on request. When well launched on some recital, he seemed to become hypnotized by the sound of his voice and raised issues and made revelations which were not altogether consistent with the impression he attempted to make at other times.

He had been born on July 28, 1905, the first of 3 children. Two brothers were living and in good health but his father had died in 1920 of heart disease at the age of 45. He had been a "converter of cotton goods" and it was from him that the patient first became interested in the textile industry. His mother, living and well at 58, had remarried in 1927 but had borne no children to her second husband. Familial diseases were emphatically denied. The patient scouted the suggestion of childhood neurotic traits, at times offering a vigorous negative before he had actually heard the examiner's question. "I am very calm, serene, even temper. Always been that way. Never ruffled. I am a healthy person," he declared. "Go through my record from A to Z. Friends, business associates." In similar fashion he disclaimed all of the exanthemata, all injuries, all operations and all serious adult illnesses, although as an afterthought he did admit to a tonsil and adenoidectomy.

He attended school until the age of 22, completing a 3 year course in textile school. During the latter part of his academic career he attended evening courses in a school of business administration in a reputable eastern university. He gave his scholastic average as "80," and insisted that he liked school "very much," played baseball both in high school and college and for a year and a half sat on a student government board. "I was just one of the boys," he stated, "I am always one of the boys. Fellow my age, though, you can't feel intimate with fellows 21, 23, 24. You feel interested in them but you can't feel too close. At least that's the way I feel. I do the best I can. I mingle with them in the barracks but I wouldn't go out of the way for some of the people I met. It's the Army, the great melting pot." He went on to contrast his school day companions: "They were all my kind. Easier to talk to and be with. Mutual interests." He admitted to rare truancy but added, "I guess that's normal," a statement which prefaced much of what he said. He failed his Regents examinations on the first attempt but qualified the following year.

The patient obtained work in a textile corporation as a "styler and fabricator" immediately after graduation. In the following 15 years he held jobs varying in duration from 2 to 4½ years with 5 different concerns, all of them textile industries. With the last 2 firms he was head buyer. In each instance he maintained that his change of employment had been by resignation and had represented an advancement either in responsibility or from a financial standpoint. He repeatedly mentioned how distressed his various employers had been at losing his services to another and at times rival organization. His income had been large and on at least 5 occasions he informed the physician that he had allotted his entire Army pay to the purchase of War Bonds. He employed tobacco and alcohol in great moderation and denied the use of drugs.

Although unmarried he was "practically engaged" to a divorcee of 37 whom he had known for the preceding 8 months. Explaining his delay in marrying he stated: "You get spoiled by too many good times, by the fine association you have with many people. You realize when you are older the mistakes you make when you are younger. I should have married while I was in college. Nice girl, but I guess I was just a little too fickle. The time just went by. My brothers are already married and have children and they are younger than me. I am still just floating around."

He spoke with romantic hesitation of a former sweetheart with whom he went for 2 years and who represented all that was femininely desirable. She, however, was a Catholic and although he arranged for her to take instruction from a Rabbi, eventually was unable to overcome his religious scruples and marry her. His one visit to a prostitute had resulted in an unsatisfactory contact, the patient being unable to obtain an erection. He had also experienced a relative degree of libidinous blocking with girl friends but never to this degree, and presented a distinctly feminine disinclination to coitus unas-

sociated with idealistic identification. "When you try to satisfy lust mechanically it isn't genuine passion. I have had no intercourse now since New Year's and it isn't anything. I have too multifarious interests whereas if you are with these young fellows it's their only interest." He denied worries over masturbation declaring: "It was never my concern. Never worried about it, never practiced it. I guess I know what it means" (laughing).

The patient's family were strictly Orthodox but he was even more rigid in his observations. He never worked on Saturday and made a point of getting home before sundown on Friday night. He followed the dietary laws and stated that he had eaten no meat since his induction 9 months previously. "The only thing I hate about this thing is I haven't been able to put on strips for the morning prayer," he declared. He had worked with a private tutor in childhood instead of attending Chedar and had continued to study with learned Hebrews until the time of his induction. He had held the office of President of a New York temple and had been a member of the administrative board of a national Jewish religious organization for 5 years.

He had always lived at home and stated that he got along well with his mother and step-father. He liked golf, the theater, dancing and "other normal pastimes"; ice skating, tennis and skiing, "all these things that we all like to do. I like cruises in the winter time. Miami in the winter time. The normal things." He claimed to read a great deal, preferring "something with depth; I don't like just plain fiction, autobiography, something with depth." He professed to collect books, although he actually bought them only for their contents. He had played the piano as a younger man but had found "no opportunity since college days."

He denied that he was or ever had been ill, maintaining that his whole problem centered upon his placement in the Army. He felt that he had never been in a branch of service in which his own particular talents could find expression and although expressing his willingness to serve wherever he might be assigned, hedged his statement by the declaration that he could not "become interested" in anything but textiles, and that a number of officers had told him he should be in the Quartermaster Corps. He had appeared before an Officers Candidate Board shortly after his arrival at the Post requesting assignment to a Quartermaster school but was rejected. His commanding officer, he stated, had made every effort to transfer him out of the Infantry realizing that he was "no soldier," and when all else failed had decided to attempt his reclassification. He had been sent to the Psychiatric Clinic with a tentative diagnosis of "neurosis" but declared he "made the mistake of putting it on too thick." He told the doctor he felt aimless, blank and hollow inside, that he was listless and that one half of him didn't know what the other half was doing. His days were "lifeless," they "weighed upon" him, and even over the week ends when he was away from camp he felt depressed and dissatisfied, brooding constantly upon his unfortunate situation. "The thought was lurking in the back of my mind even in the midst of my friends and all the confusion of this much-ado-over-nothing existence. Just filling up time." When the psychiatrist had asked him regarding suicidal notions he told him he was "betwixt and between," by which he meant that he had made no overt attempt but had frequently thought of the possibility. "In other words, my words indicted me, that's the answer I guess. I put it on too thick with the Major and he sent me to the ward."

Finding himself among psychiatric patients and being intelligent enough to realize that this inferred a great deal more than simple reclassification the patient conscientiously attempted to minimize his original statements and give an overwhelming impression of robust normalcy and hearty good health. He telephoned friends and acquaintances 1 to 3 times a day and kept up a great stream of correspondence in which he adopted a satirical approach to his hospitalization, assuring his friends that they "would surely get a laugh" out of his self-created predicament. Extracts from his letters are given below.

MONDAY AFTERNOON

"Start laughing" (watch taken away from me)

DEAR B.

Fortunately those characteristics which have been inherently imbedded in me now supply their succor and healing unto me. Placidity of disposition, a happy mien, plenty of reserve, etc. act as a solace—call it a time palliative for this unnatural life which is presently mine. Believe me—it sure strikes me funny for the while—but I'd sure loathe the idea of being confined here indefinitely. You take a healthy normal being and mix him in with some neurotics and such—peculiar changes might occur to even alter my stable being. It's interesting for a few days to dwell in such a house. Thusly—I am enabled to obtain some perspective as to the feelings—moods engendered by others who must seek their shelter here.

Reverting to how I landed here, it is certainly a case for the "Books" and I mean "The Strange Case of E. F." As you well know, my Captain realizing that my potentialities in the infantry way are nil—proposed that I be re-classified. The Captain (doctor) at the dispensary—in order to state some cause for re-classification suggested "neurotic condition." He advised me as to how I should state my case to the Major. The result of this interview, especially with reference to the wordy content on my part (I put it on too thick) landed me in this ward. Believe I have a word for it "All this and reclassification too." However, it's not worth it for too long, can you imagine the ups and "downs" that has been my course—Army-wise—and yet—how I still retain the faith that eventually I will be shifted to that branch of the service where all my "officers" feel I definitely belong. 'Tis quite an experience but I do believe I can take it. I sorta feel like a martyr here—Yet let us say—this is the Army—and strange things do occur oft-times as a result.

Would be interesting for the cause of posterity—to show my good business associates and friends a picture of myself midst these iron-bar surroundings. E. has now become Dr. Jekyll—the change from a complacent being to a harried—distracted personality. Ha. Ha. I would like to see their expressions upon being apprised of the above. (In a whisper—for fear I might take my life in my hands—am not even allowed a knife or a fork. However, one can eat with a spoon and like it.) The nurses are sure coöperative and evidence their patience with all of us *i. e.* always at our beck—call. Sh—I'm no problem—yet?

TUESDAY AFTERNOON

Time unknown

DEAR R.

Your references ("amusing and uplifting") as to the condition I presently find myself in—certainly afforded me to use the vernacular a "Kick"—aside from my mother and B. nobody is aware of that E. of "old" who now is languishing away in a hotel room (I mean a different kind of room only kinda locked in)—because all this strikes me so funny—definitely joocular in note—"Tis no strain to withstand this newly foisted way of living which has been invoked upon me. Believe though—if I was a "Victim" really allergic to some nervous disorder or call it some obsession or fixation then verily would this amount to a harrowing, nerve-wracking experience. As B. in her way describes it—as a stunt—so I gather unto myself better spirits to continue on with this hoax. Never within the stretch of my imagination or of those many friends who knew me—could I ever be pictured as a "depressed being" and no doubt B. informed you as to the ruse or method employed before I became ensconced in this strange den of mine. . . .

It's certainly a case for the Book. I believe I have a name for it—"All this and reclassification too." Be assured that I still retain those Happy Spirits, my Design for living—and above all—I can take it. It is my fervent hope that I may be reclassified and thusly shall I be enabled to do that type of work which I am best fitted for (but *never* do I want a C.D.D.—no matter if I was over age—this would apply)

Time—Thursday afternoon

Scene—Lounging around in a Ward

DEAR J.

Received your characteristically well-seasoned and spicy letter today—and whilst under the spell of its charming contents contained there-in do I hasten to answer same.

I sure would like to have seen the expression on your face when you noted the return address. Yes E. is now hospitalized—and at the same time very healthy. Quite an anomaly—but somehow that seems to be the case. This situation was affected by an interview I had with the Major regarding an obsession—which I led him to believe was a verity—Naturally you must be wondering what I'm up to now. It resolves itself to this question "whether I'm destined to remain in the infantry or be transferred unto that branch of the service—to which I would be fully devoted and at ease. Was too impressive and dramatic in dwelling upon my sad condition—with the result that immediately was I placed in a ward under observation. . . . Apparently—I who has

always been the master of words—now find myself indicted by them. With it all I cannot complain and am taking this lazy-much-ado-about-nothing existence in stride. 'Tis quite an experience to find yourself in a hospital when you're rarin'-to-go. Imagine this ever happening to me in civilian life. It seems that in the Army—at the slightest provocation—you're suspected—especially when I mentioned—"one half of me doesn't know what the other half is doing." Don't laugh too heartily. I promise you this that at our next reunion—many will be the laughs occasioned by this strange coincidence—with the help of a "few drinks" to help the story along." So why write about it—Let's give it a heading "All this and Reclassification too." . . .

The patient affected an elaborate vocabulary both in conversation and in his writing, but frequently misused words and succeeded only in ornamenting his native ingenueness with somewhat inappropriate trappings. He unblushingly declared that he was "perfectly calm and relaxed," although everything about him screamed of tension, impetuosity and barely restrained emotional and motor outbursts. He manifested a certain child like candor that prevented his disguising his real feelings even in his own interest, and in alternative phraseology admitted to essentially everything he had told "the Major" on his initial visit to the out patient clinic, with the single exception of suicidal ruminations which he completely denied. Regarding his statement that "one half of me doesn't know what the other half is doing" he explained: "You can feel so abject at times that you are sort of vacillating within yourself whether you are doing right here (pointing to one side of his trunk) or doing right here (pointing to the other side). You don't know what course to take. I used it only to emphasize the situation. It sounds ridiculous but you know what I mean. You get a kind of feeling that way sometimes."

Direct enquiry was useless with him since he replied in the negative to every query that had in his opinion the slightest overtone of abnormality. There was, however, no reason to believe that he experienced hallucinations. Projectional notions, or a systematized delusional structure were not evidenced, he most assuredly was no hypochondriac and there was at no time any flaw in his general sensorium. His intelligence was somewhat above average. He was unstable, highly keyed, precariously adjusted; a decidedly immature individual who had lost what security he had created for himself in civilian life and was genuinely out of his psychological depth in his present assignment in the Army. He had been attempting unsuccessfully to effect his own "cure," that is to re-create his civilian environment insofar as this was possible by getting into the Quartermaster Corps.

It is doubtful that this man would have come to a psychiatrist's attention in civilian life. The very defects of his personality were in some measure responsible for his material success, his "high-pressure" temperament, his lack of objectivity, his sublime assurance that he was always right. It was by no means incomprehensible that he would have continued piling up profits for his employers, earning his handsome salary and devoting himself to "normal pleasures," to religion, and to superficial love affairs for the balance of an honored and productive life. Those accidents of Fate which bring misfortune and trials to one may just as readily bring ease and comfort to another. Every reed is not leaned upon, every human defect tried in the fire. It is well for us all that this is true. E.F. was no soldier and the very roots of his personality would have been dug up in making him one, still as a perpetual civilian in uniform the Army may yet have good of him.

I have no answers to the questions raised in this paper, nor do I know where to find them. Out of my military inexperience certain possible means of simplifying and making more expeditious the tasks of the Army psychiatrist occur to me, and out of my naiveté, certain suggestions of a visionary nature regarding experience and a body of training that could make the medical officer in this field more valuable to the Army.

1. There seems to be every reason for tightening induction examinations. Every inductee could, if the machinery were suitably set up,

have a reasonably adequate psychiatric examination before taking the soldier's oath. This subject is, of course, readily expandable into another monograph. From the point of view of the present paper, the local psychiatrist would inevitably be in a better situation to pass on the health of potential soldiers in his own county or even in his own state than on the status of the men in anonymous olive drab whom he meets later in military hospitals. With certain gratifying exceptions this is not being done.

2. More careful classification of recent inductees. I cannot escape the belief that certain men have had to be discharged from the Army on psychiatric grounds who could have been useful soldiers if their capabilities and needs had been accurately understood at the beginning of their service and their placement had been more selective.

3. Greater rapidity in the administrative consummation of discharges once they have been approved by competent hospital boards. It would appear that service records could be completed with greater dispatch and that the number of hands through which the recommendation for discharge now passes before final approval could be reduced.

4. Establishment throughout the country of Recruit Reception Centers patterned after one at present functioning in a mid-Western State and headed by a commanding officer of noteworthy vision and understanding, assisted by a permanent cadre of efficient officers fully acquainted with and sympathetic to his aims. Enlisted men are quartered in small units and receive an unusual degree of personalized attention from their officers. Classification is a deliberate and careful process. Professional psychologists and college graduates who have majored in psychology, of non-commissioned rank, live in intimate contact with the men and rotate in groups of 2 for regular tours of duty on the psychiatric wards of the Station Hospital. Here they receive daily lectures from the medical officer as well as regular assignments in the investigation of patients currently hospitalized. Their records are reviewed, criticized and often made a part of the individual patient's chart. The psychiatrist is in the most intimate contact with the military training center and joins with the officers and psychologists at frequent informal conferences where both individual problems of recent inductees and general policies of the center are discussed.

5. Closer contact between line officers, chaplains and psychiatric staffs. It is at present rare for a patient's commanding officer to visit the hospital for discussion of his problem and I am afraid unheard of for a psychiatrist to go to the patient's company area in search of first hand information regarding him. The chaplain is, not infrequently, the first man whom many of the patients consult regarding their difficulties. Since there is no established military provision for this information to be passed on, it often fails to reach the psychiatrist. Regular conferences of psychiatrists, line officers and chaplains conducted for the purpose of common education might well facilitate the work of all.

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CONVULSIVE SHOCK THERAPY IN INVOLUTIONAL STATES AFTER COMPLETE FAILURE WITH PREVIOUS ESTROGENIC TREATMENT*

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AND

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THOUSANDS of patients with psychiatric disorders occurring in middle age and in involutional and presenile periods of life are constantly being treated with estrogenic substances. Many physicians believe, for example, that involutional melancholia is caused by ovarian deficiency. It is a daily incident to examine female neurotic or psychotic patients of all types from 30 to 60 years of age and hear that some doctor said their disorder was caused by "the change of life."

It has been our experience that estrogenic therapy has no value in these disorders; valuable time and large sums of money are needlessly lost; and eventually most of these patients require adequate psychiatric therapy for lasting recovery. We have therefore reviewed our records in order to compare previous estrogenic therapy with later combined psychiatric and convulsive shock therapy.

For over 25 years, many reports have indicated favorable results from administration of ovarian substances in involutional psychoses. Strecker *et al.*¹³ in 1922 reported encouraging results from use of corpus luteum and ovarian substances in involutional melancholia. Pharmacologically, these substances have been proved to be inert. More recently Werner,¹⁵ Hawkinson,⁸ Suckle,¹⁴ Mazer,⁹ Perusse,¹¹ Burlingame and Patterson⁴ have all reported favorable results. Werner¹⁵ and associates in 1934 reported not only relief of those suffering from actual menopausal symptoms and autonomic disturbances but also recoveries from involutional melancholia. Only cases treated for 3 months or longer were reported.

Burlingame and Patterson⁴ in 1941, reporting results of estrogenic treatment in 139 patients, said: "The most favorable results have been obtained in the depressions of the climacterium." Of this group, 60% showed some improvement in about 40 days. This improvement they ascribed to estrogenic therapy, although they state it was only part of the treatment employed; and yet they omit the rest of the treatment program. Davidoff and Goodstone⁵ in 1942 recommended the use of estrogens in the mild involutional psychoses which contain features resembling normal menopausal symptoms; 62% of their patients improved.

Recently, Davidoff, Reifenshtein and Goodstone⁷ reported the treatment of 60 female patients, 45 of whom were given diethylstilbestrol.

* Presented before the American Psychiatric Association, May 11, 1943, Detroit, Mich.

They concluded that their results "indicate clearly that estrogenic therapy is most beneficial in involutional psychoses of the simple type." However, they do not give their criteria for diagnosis of these cases except to call them "depressions occurring in middle life and later years without evidence of organic intellectual defects or without a history of previous depression." Neither do they give the total length of time during which treatment was administered. They do admit more than moderate discomfort from toxic effects in 22 of the 45 cases treated with diethylstilbestrol.

Danziger,⁶ who reviewed 164 such cases in the literature and added 7 new ones, gives a more critical evaluation: "Recovery or marked improvement in only 48% of a reasonable large series of adequately treated patients leaves something to be desired." He adds, "Estrogen therapy cannot be specific for involutional melancholia in the female in the present state of ability to diagnose the disease."

It is well known that spontaneous recoveries occur within about 9 months in 40 to 50% of true involutional depressions. Improvements in 60% of cases, as reported by various authors, is therefore, of no significance, especially since any treatment procedure whatever carries psychotherapeutic value. All such favorable reports tend to mislead, and, in our opinion, result from wishful thinking in therapeutic evaluation. Overwhelming factual evidence now shows that not 40 to 60% but a consistent 90% of depressive patients improve in a much shorter time with combined shock therapy and psychotherapy.

In 1938, when one of us (A.E.B.)¹ first reported consistently favorable results from convulsive shock therapy in all types of depressions, he stated: "In all previously tried chemical, endocrine or shock therapy methods, such as hematoporphyrin, estrogenic, testicular or pituitary hormones, fever therapy and narcosis, no consistent effect in shortening the course of depression has been observed." He later reported² that 90% of severe depressions, especially involutional melancholia, clear up within 3 to 4 weeks after 6 to 8 convulsive shocks. Since these reports, many have confirmed these results and the specificity of the treatment. Even the most enthusiastic supporters of endocrine therapy do not claim relief for such a high percentage in so short a time.

Ripley, Shorr and Papanicolaou¹² in 1940, and Palmer¹⁰ in 1941, have stated that endocrine imbalance is not the primary nor rarely a significant factor in the development of mental disorders. The prepsychotic personality factor and the psychobiologic makeup of the individual plus precipitating psychogenic factors are of major causal importance.

Palmer's report¹⁰ in 1941, elaborates these factors pointing out again that the potential involutional melancholiac betrays certain telltale personality characteristics throughout life. These individuals show rigidity in their personality makeup even in its earliest phases. This fundamental rigidity of personality causes resistance to psychic trauma and induces strong protective measures; such individuals lead constricted, narrow lives without mood swings or emotional upheavals. Their faulty personality traits remain the same throughout life; that

is, they may be chronically worrisome, compulsive or perfectionistic, but they do not correct or clear the mental horizon by changing mental trends. The psychotic phase is a culmination at middle age of the lifelong process and is prompted by the numerous psychic traumas of these years. Failing health, loss of productiveness, loss of relatives and friends, diminished vitality, fear of chronic organic disease, fear of sexual failure are only some of these psychic precipitating factors.

In our study, about 500 case records of psychoses and psychoneuroses occurring in female patients between the ages of 31 and 65 during the years 1937 to 1943 were reviewed. Cases which had received estrogenic hormones as therapy for the mental disorder were collected. Seventy-five consecutive cases were obtained. These individuals had all received varying amounts, usually large, of estrogenic hormones over varying periods of time without benefit. On the contrary, they frequently got worse. These patients subsequently arrived in the psychiatric department for hospitalization and rational psychiatric treatment. Of these 75 cases, 41 were classified as involutional melancholia; 12 manic-depressive, depressed type; 20 psychoneuroses with anxiety and depressed features and 2 schizophrenia.

TABLE 1.—INVOLUTIONAL MELANCHOLIA (41 CASES)

	Average	Range
Age	49.9	40 to 65
Duration of illness	1 yr. 10 mos.	1 mo. to 12 yrs.
Length of estrogenic treatment	9 mos.	1 mo. to 4 yrs.
Duration of hospitalization	47 2 days	15 to 202 days*
No. shock R	8	3 to 22
Relapses	9 (5 recovered)	
Duration and type of recovery	1 yr. 3 mos.†	3 mos. to 5 yrs. 9 mos.

* The patient in residence 202 days was given a course of theelin in oil in the hospital but made no progress over 5 weeks time. She was next started on insulin shock treatment, without progress. She was then given 22 combined insulin-metrazol treatments with considerable clinical response but she gained no insight and promptly relapsed on leaving the hospital. This case is considered a complete failure.

† Social, 12; full, 25; total, 37 (90%).

Six patients in this group showed definite increase in their difficulties with the administration of theelin. This was particularly true in those who had outspoken sexual conflicts. Five patients who relapsed made either full or social recoveries with further treatment. Four patients were considered complete failures. One patient made a full recovery and was well and active for a year, when a recurrence of depression ended in suicide. It is of interest to note that those patients treated in the years 1937 to 1940 inclusive, spent an average of 66.4 days in the hospital; while those treated in the years 1941 and 1942 inclusive averaged only 39.9 days. This decreased time suggests improved treatment techniques, including the change from metrazol to electroshock. Three patients of this group were treated with psychotherapy alone. The following case is typical of this group.

Case Study. CASE 1. J.T., female, age 47, married. The history obtained from the husband indicated that the patient was a very conscientious, meticulous, rigid personality. She had been operated on 12 years previously for

tumor of the stomach; 9 years previously she had had a cholecystectomy. Recovery from both operations was uneventful. The couple had no children but had adopted their 6 weeks old niece. The husband dated the present illness back 5 years when the patient was about 42. Their mode of living, though somewhat restricted, was entirely satisfactory including marital adjustment, until this time when the patient became mildly depressed and progressively frigid. During the last 3 years before admission she had become increasingly incapacitated because of restlessness, depression, insomnia and anorexia. For 7 months prior to admission her home physician gave weekly treatments of 10,000 units of theelin; her symptomatology increased. She was then brought to the psychiatric unit and treated with tubs, massage, vitamins and insulin for weight gain. There was no relief of the psychologic condition after 5 weeks of treatment.

Immediate affective gain followed 5 curare-metrazol treatments but on referral to an ophthalmologist for eye examination an acute panic state developed. Therefore 5 more shock treatments were given with full social recovery. However, her insight was markedly limited. At the end of a year and a half mild insomnia and complaints of inward nervousness and agitation recurred. She was readmitted to the psychiatric unit and given 5 electroshock treatments combined with curare over a period of 17 days. She was dismissed in excellent condition with considerably more insight. For the past 2½ years she has been entirely well, has done all her own housework and has assisted her husband with farm work. Recently she reported helping to harvest the corn crop, work which she had not been able to do the past 8 years. She has gained 50 pounds in weight.

TABLE 2.—MANIC DEPRESSIVE PSYCHOSIS, DEPRESSED TYPE (12 CASES)

	Average	Range
Age	46	37 to 61
Duration of illness	1 yr. 2 mos.	2 mos. to 3 yrs.
Length of estrogenic treatment	4.2 mos.	1½ mos. to 1 yr.
Duration of hospitalization	42.5 days	10 to 62 days
No. shock R	8	5 to 12
Relapses	2	
Duration and type of recovery	1½ yrs.*	4 mos. to 4 yrs.

* Social, 3; full, 9; total, 12 (100%).

The course of the patient remaining in the hospital 62 days was interrupted by 2 weeks of febrile disease. One patient in the group was treated by psychotherapy alone. Three patients showed a definite increase in their psychic difficulties with the administration of estrogens. Both patients who relapsed subsequently recovered with further treatment and have remained well. The following case is typical of this group.

CASE 2. L.B., female, age 47, single. Medical history showed pneumonia at the age of 4 and a pelvic "eviscerotomy" at the age of 45. The patient's personal history showed a stormy developmental period. At the age of 7 she lost her father by death and 5 years later, her mother. She took these losses very severely and was depressed. In school she made a good adjustment, was friendly and sociable but was obliged to give up nurses' training because of an overly-sympathetic reaction to her patients' ills. She completed business college successfully and adjusted well to a secretarial position. Her hobby was fancy and figure ice-skating with many exhibitions. In adult life she had an open, friendly personality but was inclined to be sensitive. Serious depressions followed two unhappy love affairs. A flirtation with her employer brought on a third depression together with loss of self-confidence, severe self-condemnatory ideas and syphilophobia. She was depressed, seclusive, agitated and actively suicidal with many guilt feelings over physical contacts in her skating

exhibitions and in the flirtation with her employer. Large quantities of estrone, stilbestrol and gonadogen given for a period of 1 year markedly increased the sexual tensions.

After admission to the psychiatric department and before therapy was begun, she made a serious attempt at suicide. Seven curare-electroshock treatments were followed by an excellent affective response. Intensive psychotherapy and bibliotherapy enabled her to develop good insight. She was dismissed on the 46th hospital day as fully recovered. She has maintained her recovery for the past 8 months without further treatment, is working full time and carrying on her former social activities.

TABLE 3.—MIXED PSYCHONEUROSSES (20 CASES)

	Average	Range
Age	42.5	30-69
Duration of illness	5 yrs. 9 mos.	6 wks. to 20 yrs.
Length of estrogenic treatment	1 yr. 3 mos.	6 wks. to 10 yrs.
Duration of hospitalization	38 days	15 to 84 days
No. shock R.	5	5 to 15
Relapses	2	
Duration and type of recovery	1 yr. 9 mos.†	4 mos. to 5½ yrs.

* This group consisted of 8 reactive depressions, 7 anxiety states, 3 chronic invalid reactions and 2 patients with conversion hysteria.

† Social, 10; full, 8; total, 18 (90%).

The patient whose hospitalization was prolonged to 84 days was treated with conservative therapy for 5 weeks before metrazol shock treatment was instituted. Thirty-three days after shock treatment was begun she was dismissed as a social recovery.

One patient with reactive depression following the loss of all the members of her family attempted suicide prior to admission. Under treatment she regained normal affective tone but relapsed within a 3-month period and committed suicide. The two relapsed patients were complete failures. Seven of these patients were treated by psychotherapy alone. The following case is common to this group.

CASE 3. M.M., female, age 41, married. Her medical history is typical. She "almost died" of malaria at the age of 9. At 18 an exploratory laparotomy for chronic right lower quadrant pain was done and the appendix and right ovary were removed without relief. At the age of 20 she went to a "society doctor" who made a diagnosis of a growth in the vagina and treated her with daily manual massage; she voluntarily stopped treatment upon finding out that he was a quack. At 21, the patient was again operated upon for adhesions because of continued right lower quadrant pain. Part of the left ovary was removed and a curettage was done to relieve chronic backache. Infection of the abdominal wall kept the patient bedfast for several months. At 26, the patient lost her mother. Another curettage was done for backache and the vagina was packed to push the uterus into place. When she was 28 a trip to California was prescribed for nervousness. At 35, her menstrual periods became irregular, on 2 occasions were precipitated by minor accidents. Thereafter she spent a few days in the hospital each year for various complaints.

Six weeks prior to admission to the psychiatric unit, the patient had severe insomnia, gastro-intestinal upsets and spells of nervousness. Within this 6-weeks period she used 500 three grain capsules of sodium amytal and was given 25,000 units of theelin weekly, with additional ovarian extract by mouth. The sexual history shows early sexual traumas inflicted by the patient's father and a hired man, with marked interference in psychosexual development and with subsequent poor marital adjustment and extramarital affairs. She responded rapidly to psychotherapy and was dismissed after 41 days of hospitalization markedly improved. Her excellent adjustment has persisted for over 5 years.

Two cases were diagnosed as schizophrenia of the paranoid type. From a psychiatric view, estrogen treatment was obviously not indicated. However, one patient had had surgically induced premature menopause and received estrogens for 3 years. The severe menopausal symptoms were partially controlled, but the schizophrenic reaction was not affected.

Treatment Given. On admission, patients were given exhaustive general physical and laboratory studies with a period of psychiatric observation in an attempt to establish rapport and seek conflictual material before instituting shock treatment. Of the 75 patients, 64 received some form of shock therapy but in 11 cases psychotherapy alone sufficed. Since the introduction of curare,³ its use has been routine, first with metrazol and later with electroshock to avoid traumatic complications. A course of from 6 to 8 shock treatments over a period of 2 to 3 weeks is the rule. During hospitalization adequate nutrition is rigorously managed, and in the underweight group sub-shock doses of insulin are used to stimulate appetite.

We consider the use of sedative therapy valueless; sleeping habits are carefully watched and controlled without sedation. During treatment the patient is isolated from relatives and friends. All activities, including occupational and recreational activity and bibliotherapy are prescribed individually. Following active shock treatment, patients remain in the hospital from 10 days to 2 weeks for reëducative psychotherapy. After dismissal, patients are followed through office interviews as necessary. In the occasional case of relapse the patient is readmitted or treated as an outpatient.

The consistent change in affect of these patients following convulsive shock therapy proves a near specificity of method never heretofore seen in psychiatric therapy of these disorders. However, it has been found that many patients have relapses or recurrence of their disorder at a later date unless psychogenic problems have been solved by psychotherapy. It is a necessary adjunct to shock treatment.

We no longer consider convulsive shock therapy dangerous in the presence of cardiac disease, arteriosclerosis, or changes due to the aging process, when curare is used to soften the convulsive seizures. While hazards are increased by these factors, softening the convulsion certainly minimizes the strain upon skeletal, visceral and vascular systems.

Conclusions. Seventy-five consecutive cases of midlife and involutional mental disorders were obtained from the study of about 500 case records. All of these had received varying amounts of estrogenic hormones without benefit.

This series was treated with convulsive shock therapy and psychotherapy or with psychotherapy alone, combined with thorough psychiatric supervision. Under this treatment, 90% showed social or full recovery in 4 to 6 weeks.

Estrogenic hormones have no place in the treatment of psychiatric disorders except for symptomatic relief of vasomotor symptoms. Convulsive shock therapy is a near specific for the relief of all types of affective disorders, especially involutional melancholia.

These facts need wider dissemination before the general and psychiatric professions to save time and expense of needless non-scientific treatment in this misunderstood group of patients. Estrogens should further be condemned because they may be harmful and often make the psychiatric disorder more severe.

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THE ENDOCRINE FACTOR IN HOMOSEXUALITY

REPORT OF TREATMENT OF 4 CASES WITH ANDROGEN HORMONE

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It is now realized that homosexuality is very widespread among all classes of society and furthermore that it is apparently on the increase. According to some authors, its increase seems to have paralleled the growth of civilization. Thus Alfred C. Kinsey³ states "that something between one-fourth and one-third of all the males in any mixed-age group has had some homosexual experience." Among primitive peoples and savages, homosexuality appears to be almost non-existent.

Various theories have been presented to explain homosexuality. The explanations proposed have varied from the purely physical to the purely psychologic. Krafft-Ebing⁴ believed in the hereditary basis while Hirschfeld² proposed a "psychoglandular" condition as the underlying factor. Freud¹ postulated still another theory: namely, that homosexuality in substance was the result of an imperfect or abnormal solution of the Oedipus complex and castration complex in the case of the boy and of the Elektra complex in the case of the girl. Many of Freud's disciples have suggested considerably different views.

However, they all agree that the psychodynamic approach to the study of homosexuality tends to show the importance of the psychosexual experiences of childhood in determining the future sexual behavior of adolescents and adults. In particular, according to most psychoanalysts, the development of the homosexual can be traced back to the unwholesome personal relationships between parents and their children existing in the home.

It would take us too far afield to present all the objections and criticisms that have been raised against this point of view. Suffice it to say that even Freud finally admitted that in many cases of homosexuality a constitutional (endocrine) factor is present.

Homosexuals have been usually divided into two broad groups, overt and latent. The overt homosexual, as the name implies, is one who has committed homosexual acts. The latent homosexual is one who has not as yet committed any homosexual act but whose behavior can only be explained on the basis of repressed homosexual drives. Such individuals as a rule, sooner or later, resort to overt homosexual practices.

Probably a better classification and one that might avoid some of the criticisms directed at the purely psychoanalytical concept of homosexuality is that of innate and acquired. The psychopathology of acquired homosexuality may be correctly explained on the psychoanalytic basis as outlined by Freud and his disciples. The condition of the innate homosexual, on the other hand, can be best explained on the basis of the presence of a somatic factor in the form of an endocrine disorder.

Anthropomorphic studies as well as endocrine studies have not revealed a specific body structure that is characteristic of the homosexual. On the other hand, the passive male homosexual has certain mannerisms of speech and gait and actions that stamp him as "*sui generis*." The "fairy" is easily recognized. To a lesser extent, the same is true of the masculinized female homosexual. These structural changes are readily correlated with disturbances in the functioning of the endocrine glands, principally the pituitary gland and the gonads. In this connection, the studies of the androgen-estrogen output of homosexuals have been very illuminating. Thus Neustadt and Myerson,⁶ in a quantitative sex hormone study of 29 overt homosexuals, found a marked disturbance in the normal androgen-estrogen ratio. The deviation from the norm took one of two directions: (1) a decrease in the androgens combined with a normal amount or excess of estrogens; or (2) a normal amount of androgens combined with an excess of estrogens.

The experiments of Young and Rundlett⁸ may also be cited in this connection. These experimenters produced homosexual activity in spayed female guinea pigs by treatment with estrogen and progesterone.

In the case of the innate homosexual, the endocrine factor is predominant. As a result of the endocrine dysfunction, the individual develops abnormally both structurally and functionally. His physiologic and psychologic functionings become markedly disturbed with

resultant distinctive abnormal behavior. The direct effects of the endocrinopathy, therefore, is to cause the individual to stand out as a sexual deviate. However, in addition to these direct effects, there may be indirect effects which may still further modify the individual's behavior and personality.⁵ These indirect effects are dependent upon the individual's emotional reactions to his own deficiencies. How the individual will react in such a case will naturally depend upon his previous emotional and social experiences. Hence, no two individuals will necessarily react in the same manner to the same defect.

The fact that there is usually a diminution in the secretion of the androgen hormone in male homosexuals has strengthened the belief of the importance of the rôle of the endocrine factor in the causation of homosexuality, and has given impetus to the possible therapeutic value of the male sex hormones in the treatment of such cases. The homosexual is an unadjusted individual. Every homosexual act is a delinquent act and is so labeled by society. The homosexual very often also becomes involved in criminal acts of the most sordid type. Any treatment that offers relief in these apparently hopeless cases is worthy of a trial. There have been many reports in the literature concerning treatment of homosexuals with various endocrine preparations. Some of the earlier reports of the results of this type of therapy were unfavorable. The recent reports, however, are much more encouraging. The better results may be due to the fact that more active and potent preparations of androgen hormones are now available.

Thus, for example, C. A. Wright⁷ reports the results of endocrine treatment in 14 male homosexuals. The hormone assays in all cases showed a very marked diminution. After treatment, with androgen hormones, however, they all showed an increased androgen output. Coincident with this change, an improvement was noted in the sexual behavior of 9 of the patients, 3 of them claiming to have become normal. Four reported improvement from other causes than the endocrine treatment. One reported no improvement.

The following 4 cases are reported to show the effects of androgen hormone therapy in adolescent male homosexuals.

Case Studies. CASE 1. W.H., a white boy aged 15 years, 9 months, was referred to the Child Guidance Home for observation because he was a serious delinquent. His delinquencies had started a year previous to his admission. At that time, he burglarized a home. From then on his delinquencies increased in frequency and in magnitude. He was brought to court for the first time because he had run away from home and had been involved in a hold-up. In addition, he had presented a problem at school for a considerable period of time. He truanted frequently and his academic achievement was not on a par with his intellectual capacity.

The boy's developmental history was essentially normal. He had had the ordinary diseases of childhood, but apparently with no serious complications.

The parents described William as being personally very clean, meticulous, and particular. He was interested in athletics and enjoyed swimming, fishing and camping. He never had many friends and never any close friends. He seemed to prefer the seclusion of his own company. He had never shown more than a casual interest in girls. Although he knew how to dance, he made no effort to go to dances or to parties. When he was about 14 years of age, he made the acquaintance of a boy his age to whom he became closely attached.

At home he was very domineering and insulting. He came and went as he pleased and when questioned, threatened to run away. He had always been subject to temper tantrums.

Even in grade school he was considered sneaky, insincere, untruthful, underhanded and impudent. He showed no interest in his work, but always managed to pass. In high school, he was also difficult to control and showed an immature type of behavior. When thwarted, he would resort to temper tantrums in the classroom. On several occasions he carried a loaded gun to school.

It was during his high school days that he began to rob and steal. The delinquencies in which he was involved have apparently always been in the company of his one close friend whose acquaintance he made at high school. On one night, the two boys burglarized 5 homes. Very often they remained away from home all night sleeping in the woods.

When apprehended by the police, the boy was very sarcastic, insolent and arrogant. He threatened to shoot certain people at the first opportunity. This applied especially to the police and his parents.

The social background in this case was apparently of the best. The father was a highly intelligent man who had always been a good provider. He was earning about \$10,000 a year. He was greatly concerned over his son's anti-social behavior, but was unable to offer any explanation for it. He had always been under the impression that their relationships had been very good and could not understand why the boy had turned against him. He was completely bewildered at the turn that events had taken. He reiterated over and over again that the boy had everything he needed at home and therefore there was no reason for his stealing.

The mother was a personable individual who made a very good impression. She appeared kind and firm. It was apparent that she was the disciplinarian in the home. She appeared to be emotionally untouched by her son's difficulties. The home atmosphere was congenial, the only quarreling occurring between the patient and his younger sister. The latter was a very intelligent girl who presented no problem either at home or at school.

The physical examination of the boy, including the neurologic examination, was essentially negative. The urinalysis, complete and differential blood count, blood Wassermann, and tuberculin tests were all normal.

The endocrine examination revealed a hypogonadal status. The boy showed the eunuchoid type of skeletal development. He was 69 inches tall (2 inches above the average for his age) and his span was even greater, being 72½ inches. Interestingly, his bone age was only 14 years, showing that he had great possibilities for continued linear growth.

His voice was still high-pitched and there was no sign of a beard on his face. His gait and mannerisms were effeminate. The genitalia were exceptionally large with a female hair line. Basal metabolic readings were minus 2% and minus 5%. The glucose tolerance results were as follows: 106 mg., 131 mg., 93 mg. and 90 mg.

On the Standard Revision of the Simon-Binet test, the boy received an intelligence quotient of 120, thus rating him as an individual of superior intelligence. In his answers, however, there was a wide scatter of successes and failures, which was highly significant in view of his social immaturity which was startlingly shown when he was tested on the Vineland Social Maturity Scale. On this scale, he rated as sub-average, his social quotient being 82.9.

The behavior of the boy while at the Child Guidance Home was that of an immature, effeminate and indecisive person. He was shy and timid and at first tended to withdraw from the group. He never engaged in any boys' games. Later he became very friendly with the much smaller and younger boys to whom he began to boast about his escapades. He bragged about the number of robberies he had committed and stated that there was no need to be afraid of committing such acts if one carried a gun. He also boasted about his pipe-smoking but privately admitted that it made him sick. He annoyed the younger boys by his attempts to kiss them and to fondle them. On several

occasions he and another boy were found in compromising positions in the dormitory. Another effeminate boy who was being studied at the Home stated that William masturbated frequently, trying to get the other boys to perform various perversions with him, especially fellatio. He even offered to pay for this service. When one of the older and more masculine boys became ill, William insisted on nursing him. He sat on his bed and ministered to the sick boy's needs in a very motherly and loving manner. In general, in his social relationships he could be described as a highly demonstrative, dependent woman.

In the course of interviews, William admitted that he stole because he wanted lots of money and "to bolster my courage." The year before his arrest he had formed a friendship with a very masculine boy of his age who was "very brave and had a great deal of courage." With this boy, William was involved in 30 stealing episodes. William never stole alone. In connection with these episodes, Bill obtained a gun. He admitted that "guns frighten me" but he felt that by "carrying a gun he proved himself to be a man." He and his partner in thefts used to go out on frequent bicycle rides. He admitted that both would masturbate as often as every half hour during these trips. His partner was particularly active. He also stated that his friend had had intercourse but "I get no pleasure out of fooling around with girls." This was said with a great deal of disgust. It was evident that the other boy was the leader and both reckless and fearless while W. was really afraid. W. was extremely jealous of his chum and objected strenuously to the latter associating with other boys.

Another reason advanced by W. for carrying a gun was the fact that he had been frequently accosted by men, especially colored men, who demanded that he perform fellatio on them. It was later brought out that the probable basis for this statement was that his dream life as well as his phantasy life were full of just such adventures, especially of being attacked by negroes.

It was also brought out that he was scared every time he committed a theft, or burglary, but that it was "fun to be scared this way." It gave him the same thrill that he had following an ejaculation.

From additional material elicited during many interviews it was evident that the boy was suffering from the fear of castration by his father. This was an ever-present threat to his security, causing a great deal of anxiety and the constant need to prove to himself that he was still a male. From the psychodynamic standpoint; therefore, some of his behavior could be considered as a compensatory mechanism by means of which the boy attempted to prove his masculinity.

Basically, however, it was apparent that the boy, because of the gonadal imbalance, was an innate and latent homosexual.

Treatment with androgen hormone was commenced. The boy received deep intra-muscular injections of 25 mg. testosterone propionate* 3 times a week for a period of 6 months, after which they were given twice a week for 3 months, and then discontinued entirely.

The results were startling. A decided change was noted in the boy's personal appearance. There was a growth of hair on the face and in the axillæ. The hair on the mons assumed the male configuration. His voice became deep. Interestingly, whereas before treatment he had shown a rapid linear growth, there was a marked lessening in this respect following treatment.

Coincident with these structural changes, there was a marked change in his personality. Instead of a fearful, highly emotional and demonstrative effeminate boy, he became a pleasing type of the aggressive male. There were no more delinquencies. His sexual life also became normal. He fell in love with a girl to whom he later became engaged.

At last reports (4 years after treatment) he was in the armed service of his country where he has made a perfect adjustment.

At no time during the course of treatment was any attempt made to treat

* Neo-Hombreol, supplied through the courtesy of Roche-Organon, Inc., Nutley, N. J.

the boy psychoanalytically. Psychotherapy was limited to the explanation of the rationale of the use of endocrine medication in his case.

CASE 2. C.R., a white boy of 13, was referred for study to the Child Guidance Home because he had been involved in a series of petty thefts at school. The first stealing episode had occurred 2 years previously, at which time the boy had stolen milk from porches of persons living in the neighborhood. He had also taken 41 books from the school library which he never returned. Various other minor thefts were also reported. In addition, it was noted that he did not associate with other children at school. He kept aloof and showed definite tendencies to withdrawal.

The family history, while not unusual, was interesting. The home was a broken one, the father having deserted when the patient was 3 years old. All the children, of whom there were 5, were placed in a Children's Home. C. who was the youngest remained there for 3 years, which was a considerably longer period than that which his brothers and sisters had stayed. On his return home, he became extremely devoted to his mother, helping her with all her household tasks. The other children immediately nicknamed him "sissy." There was a great deal of financial distress in the home, the economic status being most often just marginal.

According to the personal history, the boy was a premature baby, weighing 3 pounds at birth. His developmental history was entirely normal and no unusual medical incidents had occurred.

In general, the physical examination was essentially negative. The blood Wassermann was negative. The endocrine picture was very suggestive. The boy was of average height but 15 pounds overweight. The fat distribution was principally of the mons-mammary-girdle type. There was no hair on the face or in the axillæ. The genitalia were small, with sparse hair present on the mons veneris. Two basal metabolic readings gave the following results: minus 19.5% and minus 18.2%. His sugar tolerance was definitely increased, the readings on the glucose tolerance test being fasting blood sugar 88 mg., first specimen 121 mg., second 94 mg., and third specimen 87 mg.

On the Stanford-Binet test, C. received an intelligence quotient of 99, ranking him as a boy of average intelligence.

At the Child Guidance Home, it was noted that C. was very effeminate. He talked in a high-pitched girlish voice and walked with a mincing gait. His face was round and his cheeks were rosy. He was extremely neat about his person and always looked clean and well dressed. He did not engage in any rough play with the other boys. He was very easy-going and very seldom asserted himself. He was tractable and easily managed. He had a huge appetite and drank a great deal of water between meals. He always asked for milk. He appeared extremely phlegmatic and very sleepy. He yawned constantly. These characteristics were so marked that he was often asked if he felt ill or tired. He preferred being by himself. When he was alone, he usually sat down and read fairy tales. He was ashamed of this sort of reading but persisted in it nevertheless. He appeared to daydream a great deal. An interesting fact about his fantasy life was that his mother always appeared in them. An outstanding characteristic of his fantasies about his mother was that she usually lived to be 300 years old. The boy admitted that he worried a great deal about his mother. She was hard of hearing and he was very much afraid that she might some day go out on the street and, because of her deafness, meet with a fatal accident. He did not know what he would do without her. He was greatly attached to his mother and was very jealous of his sister when his mother made a fuss over her. It was also brought out that the boy still slept with his mother and until recently would often sit on her lap. The mother, on occasion, sat on his lap. The mother admitted that the boy slept with her, but in extenuation said that she always looked upon him as a girl. When C. was questioned about sex, it was discovered that he was well informed, but that sex as such held very little interest for him. He admitted that he had masturbated occasionally.

In reviewing the findings, it was felt that the boy's asocial and antisocial

behavior was due to both exogenous and endogenous factors. From the psychodynamic standpoint it was apparent that the desertion of the father with the resultant placement of the boy in an orphanage plus the continuous economic stress in the home had given the boy a marked feeling of insecurity. The feeling of insecurity was further heightened by the fact that his only anchorage, namely his mother, was sick and physically handicapped and therefore might be suddenly taken away from him. The economic and social and emotional deprivations could thus readily account both for his antisocial behavior and for the obvious mother fixation.

However, the boy's endocrine condition could not be overlooked. The boy's personality make-up was definitely in line with his glandular make-up. He was sleepy and tired all the time. It was difficult to arouse him in the morning. The boy was sluggish both mentally and physically. That is why he hated school despite the fact that he was of average intelligence. In addition, he was shy, timid, effeminate and lacking in aggressiveness. All these traits are characteristics of the adolescent male suffering from dystrophy adiposo-genitalis. Additional physical characteristics of this glandular disturbance are the increased appetite and abnormal thirst. In this case the boy loved to drink milk and his petty thievery was essentially limited to stealing milk. In other words, his stealing was not that usually associated with hostile aggressive type of behavior. Rather it was a reaction called forth by an inner elemental urge due to a pathologic condition.

The psychopathology in this case, therefore, apparently involved situational factors as well as endocrine factors. It was felt that the boy would profit from psychotherapy and endocrine therapy. Both were recommended, but unfortunately neither was carried out.

Three years later, the boy was returned to the Child Guidance Home with almost the identical complaints. His truancy from school was chiefly stressed. At this time, C. presented a somewhat different picture than the one he had when he was first studied. He had gained markedly in weight and his responses were very slow. His effeminate appearance was even more pronounced than before. He giggled, smiled, rested his hands on his hips, rolled his eyes and tossed his head and expressed indignation exactly the way a girl does. He wore a bracelet which he himself had made. While sitting in the chair, he swung his hips about and held his head in his hands, saying, "Oh! dear, Oh! dear," every time he was asked a question.

Reexamination of the boy showed that in the past 3 years the boy had gained 42 pounds in weight and had grown 7 inches in height. He was 27 pounds overweight for his height which was average. His face was round and plump. There was no hair on his face. His general appearance was that of a girl. His breasts were large and his hips broad and rounded. The excessive fat was distributed principally over the hips and thighs. The genitalia were normally developed, but the hair over the mons had the female configuration. His B.M.R. was -3% and the glucose tolerance test gave the following readings: fasting blood sugar, 117 mg.; first specimen (often 100 gm. glucose), 121 mg.; second specimen, 121 mg.; third specimen, 95 mg. According to the androgen assay, he secreted 8 I.U. in 24 hours.

In interviews with workers, the boy spoke of his truancy and said that he hated gym because he was ashamed of his body. That was why he played hooky from school. He realized that he was built like a girl. He admitted that he was afraid to play with boys of his age and, although he resented being called a "sissy," he realized that it was a proper nickname. He wished he could be born over so that he could start all over and be a real boy. He denied having had any sex experiences or having practiced any sex perversions. He still slept in the same bed with his mother. Although he went with girls who permitted all kinds of liberties, he never took advantage of his opportunities. He said that he had never had the desire for sexual intercourse. He loved nature, art and good music. He had a passive, submissive, effeminate type of personality.

It was apparent that the boy had insight into his condition and as a result

had developed a marked feeling of inferiority. This had caused him to seek escape by withdrawing from normal social contacts. The latent homosexual trends were also becoming more and more noticeable.

In view of the outstanding importance of the glandular condition, treatment with testosterone propionate was commenced. The boy, however, was uncooperative, and did not report regularly for his treatments. He became involved in overt homosexual practices for which he was finally apprehended by the police. The boy was terribly mortified and attempted suicide. He wrote a note to his mother in which he said that he knew he was different from other boys and therefore hated and despised himself. All he thought of was suicide.

The boy was urged again to try medical (endocrine) therapy. He consented and this time he cooperated fully. The results were highly gratifying.

His body build soon changed. He lost in weight and his appearance became more rugged and manly. Hair grew on his face and in the axillæ, and the pitch of his voice was definitely lowered. Coincident with these physical changes, there was a change in his personality traits. From a shy, timid, self-effacing, effeminate looking individual he became an aggressive male adolescent. At present he is in the armed forces where he has made a good adjustment.

CASE 3. L.B., a white male age 22, was referred because he was extremely nervous. His nervousness took the form of marked instability, hysterical spells and temper tantrums. He was easily angered and often "felt like screaming." When thwarted, he pouted or had temper tantrums during which he would "break things." According to the patient he had been nervous all his life.

The patient was a very slender young man. He was 67 inches tall and weighed 109 pounds. His gait and mannerisms were definitely those of a girl. His voice was very high-pitched.

The general physical examination was essentially negative. The pertinent endocrine findings showed that he had a eunuchoid type of skeletal development. His skin was smooth and fair. The hair was soft and wavy. There was no hair on the face or in the axillæ or on the chest. The genitalia were normal in size but there was practically no hair on the mons veneris. The cremasteric reflexes were absent. The prostate gland was easily palpated. His B.M.R. was -4%, and his androgen output was 10 I.U. in 24 hours.

In conversations with the patient, it was learned that he was attending a school in order to become a "beautician." He "just loved" to beautify women and he thought that it was "marvelous" to be able to make a coiffure. He thought his nervousness was due to the fact that he had a high-pitched voice. He was very conscious of this and justly so. His voice was definitely that of a girl. He had had to listen to the taunts of his friends about his being a girl but, although he raged inwardly, he felt that there was nothing he could do about it. The jibes and jeers were all the more pointed because of his feminine mannerisms and gait. His choice of occupation only served to enhance his female characteristics.

The patient had always been aware of his deficiencies and, as a result, had developed a marked feeling of inferiority and insecurity. At home, the situation was aggravated by the fact that his father had openly rejected him. The father admitted that he was disappointed in his son who from childhood had never shown any inclination to be a "real boy." He had never played baseball or football, neither had he taken part in any sport that was considered rough. His lack of virile masculinity had always been outstanding. The patient admitted that he occasionally had an erection but these occurred very infrequently. He masturbated now and then but he was not certain if there was any emission. There was absolutely no sexual urge. He liked pretty women, but only in the same manner that one liked a beautiful picture. He told with some signs of pride that he had been keeping steady company with a girl but, on questioning, admitted that there had been no sex play between them. In fact, in the 4 years that he had been calling on the young lady, he had not even kissed her once. He claimed that he liked her because she had pretty hair and her hands were very beautiful. Men had made advances to him but he was

both afraid and repelled by their roughness. However, he did confess rather reluctantly that certain men did appeal to him, but he could not exactly describe the emotional state aroused in him by them.

The patient was given deep intramuscular injections of 25 mg. of testosterone propionate every other day for several months. Gradually various changes were noted. Hair began to grow on the man's face and chest as well as in the axillæ and over the mons veneris. His voice began to break. All the symptoms of beginning puberty appeared. The patient reported more frequent and longer erections and later an occasional nightly emission.

Coincident with these developments, there were marked changes in his attitude and behavior toward the opposite sex. He reported that for the first time he was beginning to notice and to comment on the various physical charms of the girls with whom he came in contact. Stranger still, he felt an urge to touch them and to embrace them. His "fiancée" was rather amazed and provoked at his description of the sex allure of the various girls at the beauty parlor where he worked. He atoned for this by becoming more amorous and attentive toward her. For the first time he understood and appreciated the innuendoes in the risqué stories that his fellow workers told. Little by little, as his treatment progressed, he became more and more masculine both in his appearance and in his behavior. One day he announced that he was disgusted with his work; that hair setting was a job for girls and that he would obtain work that was manly. This he proceeded to do. Shortly thereafter he was married. His sex life has been perfectly normal. At the beginning of treatment examination of the semen failed to reveal the presence of active spermatozoa. However, as treatment continued, this condition was rectified and his wife soon became pregnant.

CASE 4. R.O., a white boy of 13 was referred by his family physician because of his effeminacy. In school, the other boys called him "sissy" because of his feminine mannerisms, actions, and high-pitched voice.

The personal social and family histories were essentially negative. The same was true of the general physical examination. The endocrine examination revealed the following pertinent facts:

The boy had the female type of skeletal development; the pelvis was broad and he was knockkneed. His waist was extremely small, and his fingers were long and delicate. His skin was fair and smooth. His face was very feminine looking, the skin being very fair and highly colored. There was no hirsutism either on the face or in the axillæ. His breasts were exceptionally large. The penis and testes were normal in size but there was a female hair line.

Androgen determination showed a secretion of 7 I.U. in 24 hours.

From interviews with the boy it was learned that he realized that he was not as masculine as most boys and that he had tried to compensate for this by forcing himself to become interested in athletic sports. In this he had not been very successful. He was more successful in amateur dramatics. He liked to study and was on the honor roll in his class. When younger he played only with girls. He helped his mother with the household tasks and particularly enjoyed helping with the cooking and baking.

At the age of 10 he began to have nightly emissions. These were accompanied by vivid dreams. In these dreams a naked man who was being whipped unmercifully by another man would appear. The boy used to look forward to these dreams, as they gave him a great deal of emotional satisfaction. He did not understand the nature of the emotion that was thus aroused. The men in the dreams were always big muscular broad-shouldered individuals with slender waists.

For the past year he had begun to masturbate during these dreams. Recently the dreams varied somewhat from the original dreams in that the one naked man tortured the other by either burning his penis or by sticking pins into it.

He admitted that several times he had seen boys and men of this particular build naked and that they had aroused a strong sexual urge in him. Girls never aroused him in that manner. He had often seen his mother in the nude but she had never aroused any sexual desire in him.

Although he had been greatly aroused on various occasions by the sight of nude boys and men, he had always been able to restrain himself from embracing them. Such sights, however, would produce strong erections and a great desire to masturbate.

The boy had practically no knowledge of the anatomy of the female sexual organs nor of the physiology of sex in general. He did not know how the sexual act was performed.

Treatment with testosterone propionate was instituted. Injections of 25 mg. were given 3 times a week. As improvement was noted, the injections were gradually reduced to twice a week. Recently they were discontinued altogether.

The first improvement noted was a change in the pitch of the boy's voice, which became much lower. Hair began to grow on his face and gradually his whole physical contour changed. He lost his feminine curves and his breasts became smaller. The boys stopped calling him "sissy" and began to cultivate his friendship.

Interestingly, he told that, coincident with these structural and personality changes, the content of his nightly dreams had changed. He began having dreams with heterosexual content. A woman entered into the dreams: at first she merely undressed the man and admired his slim waist and muscular build. In succeeding dreams, the woman also undressed. The man would touch her breasts and then they would both go to sleep. These dreams did not excite him and never led to orgasms.

After 6 months of treatment, he began to feel a thrill when standing next to a girl. He noticed that he desired the company of girls more and more. Boys did not thrill him any more in the manner they had formerly. When finally discharged, he was in all respects, a normal male.

Discussion. The need for the psychosomatic approach to the study of homosexuality is demonstrated in the 4 cases that have been presented. Or rather, the term somatopsychic should be used as heretofore, the psychic component has been overemphasized in discussions of the etiology and pathology of homosexuality. The somatic or constitutional factor has not been sufficiently stressed.

If we employ the suggestion of dividing homosexuals into two groups, innate and acquired, it will be seen that these 4 cases can be classified as innate homosexuals. Only one of them had resorted to overt homosexual practices before treatment was commenced. The homosexual trends and drives of the other 3 were obvious and unmistakable. Obvious also was the fact that their innate homosexual drives were due to endocrine dysfunctions. As a result of disturbed gonadal secretion, the boys failed to develop normally both structurally and functionally. Their resultant behavior was such that it stamped them as sexual deviates of the homosexual type. This represented the immediate and direct effects of the endocrinopathy upon the patient's behavior and personality.

In addition to these direct effects, however, there were indirect effects which varied in each case. These indirect effects on the patient's behavior and personality were due to their emotional reactions to the awareness of their own physical shortcomings.

These emotional reactions are very important, as they often furnish the motivation for the individual's behavior toward his social milieu. Very often such motivations are operative at the unconscious level.

How an individual will react to the awareness of an organ deficiency will depend largely upon his intellectual and emotional endowment

and upon the nature of his past experiences. Hence, no two individuals need necessarily react in the same manner to similar defects. This is well illustrated in Cases 1 and 2. Both of these boys were aware of the fact that they were different from other boys in certain specific respects. Each, however, reacted differently to this knowledge. W.H. (Case 1) reacted to his lack of masculinity by developing a marked feeling of inferiority and insecurity for which he tried to compensate by assuming an attitude of superiority. By adopting the rôle of a bandit and gunman, he hoped to prove his masculinity both to himself and to the world.

C.R. (Case 2) also realized his lack of masculinity and also developed marked feelings of inferiority and insecurity. However, his reaction to this situation was different from that of W.H. (Case 1). Instead of compensating for his feeling of humiliation by developing a hostile, aggressive type of behavior, he became neurotic. His neuroticism manifested itself in various ways, culminating finally in an attempt to escape from reality, first by merely withdrawing from all social contacts and, when this failed, by attempting suicide.

Similarly the choice of occupation by L.B. (Case 3), namely that of hair stylist, can be looked upon as an indirect effect of his gonadal insufficiency.

The differences in the reactions of these boys to the knowledge of their constitutional deficiencies can only be explained on the basis of the differences in their past social and emotional experiences. The importance of these indirect effects can not be overemphasized, as very often they furnish the leitmotif for the individuals reactions to his social milieu.

In all 3 cases, treatment with testosterone propionate brought about both structural and functional changes with resultant disappearance of both the direct and indirect effects, and the development of normal masculine attitudes and trends.

Similar results were obtained in Case 4. In this case, as a result of treatment with androgen hormone, the latent homosexual trends were gradually converted into normal heterosexual equivalents.

Conclusions. Four cases of male homosexuality are discussed and the need of the somatopsychic approach to their understanding is stressed.

The division of homosexuality into innate and acquired is suggested. The importance of the endocrine factor in the former is discussed and the beneficial results of treatment with testosterone propionate in 4 such cases are reported.

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SULFAMERAZINE (2-SULFANILAMIDO-4-METHYLPYRIMIDINE)***II. SULFONAMIDE CONCENTRATIONS IN THE BLOOD OF MAN PRODUCED BY SMALL, DAILY, ORAL DOSES OF SULFAMERAZINE, SULFAMETHAZINE, SULFADIAZINE, AND SULFATHIAZOLE**

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PHARMACOLOGICAL and clinical studies of sulfamerazine^{3,5-12,15,17,21} have shown that, following oral administration, a higher concentration in the blood is attained more rapidly and maintained longer than the concentration produced by various commonly used sulfonamides in equal doses. These characteristics of sulfamerazine result from its rapid absorption from the alimentary tract and its slow excretion by the kidney.²¹

The experiments reported herein were designed to permit a comparison of the concentrations of sulfonamide produced in the blood of normal human subjects by the daily administration of a single small dose of sulfamerazine (*2-sulfanilamido-4-methylpyrimidine*), of sulfadiazine (*2-sulfanilamidopyrimidine*), of sulfamethazine (*2-sulfanilamido-4,6-dimethylpyrimidine*), or of sulfathiazole (*2-sulfanilamidothiazole*).

Methods. Eight apparently normal, male laboratory workers, whose weights varied from 55 to 77 kg., were given initially a 2 gm. oral dose of sulfonamide. This was followed by daily doses of 1 gm. each during the succeeding 5 or 6 days. In one series the initial dose was 1 gm. and the sustaining dose 0.5 gm. per day. In each case the initial dose and the daily maintenance dose were given at 8:30 A.M. Using the method of Bratton and Marshall,¹ the concentration of "free" sulfonamide in 0.1 to 0.3 cc. of whole blood was determined at frequent intervals, and the concentrations of "free" and of "total" sulfonamide were determined on one or two 24-hour samples of urine from each individual. Total leukocyte counts were made at the end of the period of higher dosage with sulfamerazine, and at the beginning and end of the dosage periods with sulfadiazine, sulfamethazine and sulfathiazole, in which order the drugs were studied. At least 1 week elapsed between the final dose of one series and the initial dose of the next series.

Results.—In Table 1 are presented the average sulfonamide concentrations in the blood, together with their standard deviations.

* Sulfamerazine was originally termed sulfamerizine.

Although blood levels of 0.5 mg. or less per 100 cc. could not be measured with accuracy, these are included in the averages since their occurrence was rare, except 24 hours following sulfamethazine or sulfathiazole administration.

TABLE 1.—AVERAGE CONCENTRATIONS* OF FREE SULFONAMIDE IN THE BLOOD OF 8 NORMAL MEN FOLLOWING SINGLE DAILY DOSES OF SULFAMERAZINE, SULFADIAZINE, SULFAMETHAZINE, OR SULFATHIAZOLE

Day	Hours†	Hours‡	Sulfamerazine		Sulfadiazine	Sulfamethazine	Sulfathiazole
			Initial dose, 2 gm. Daily maintenance dose, 1 gm.	Initial dose, 1 gm. Daily maintenance dose, ½ gm.	Initial dose, 2 gm. Daily maintenance dose, 1 gm.	Initial dose, 2 gm. Daily maintenance dose, 1 gm.	Initial dose, 2 gm. Daily maintenance dose, 1 gm.
1	..	1	5.6 ± 2.7	3.7 ± 1.2	1.3 ± 0.6	5.9 ± 1.6	2.7 ± 1.8
		2	6.7 ± 2.4	4.6 ± 0.9	2.2 ± 0.8	6.6 ± 1.8	3.8 ± 1.5
		4	7.1 ± 1.6	4.6 ± 0.8	2.7 ± 0.7	5.6 ± 2.0	4.1 ± 0.6
		8	6.3 ± 1.3	4.1 ± 0.7	2.5 ± 0.7	3.8 ± 1.9	2.0 ± 0.5
2	0	24	3.6 ± 1.2	2.1 ± 0.7	1.1 ± 0.2	1.3 ± 0.9	0.4 ± 0.1
3	0	48	3.4 ± 1.4	1.9 ± 0.8	1.2 ± 0.3	0.7 ± 0.6	0.2 ± 0.1
5	0	96	3.3 ± 1.4	2.0 ± 0.8	1.1 ± 0.4	0.6 ± 0.5	0.2 ± 0.1
	2	98	6.3 ± 1.5	4.0 ± 1.2	2.6 ± 0.7	3.8 ± 1.3	1.9 ± 0.6
6	4	100	6.7 ± 1.6	4.3 ± 1.0	3.5 ± 0.5	3.0 ± 1.5	2.1 ± 0.4
	0	120	3.1 ± 1.0	1.9 ± 0.7	1.3 ± 0.3	0.6 ± 0.4	0.3 ± 0.2
	2	122	5.0 ± 1.3	4.2 ± 0.9	3.3 ± 0.9	4.3 ± 1.2	2.1 ± 0.8
	4	124	6.2 ± 1.3	4.2 ± 0.5	3.8 ± 0.7	3.4 ± 1.4	2.1 ± 0.2
7	0	144	3.3 ± 1.4	2.3 ± 0.9	1.3 ± 0.4	0.5 ± 0.4	0.3 ± 0.2
	2	146	6.0 ± 2.0	4.0 ± 1.2	3.0 ± 1.0		
	4	148	6.7 ± 1.7	4.1 ± 1.1	3.4 ± 0.6		
	8	152	6.1 ± 1.7	3.5 ± 1.1	3.1 ± 0.7		
8	24	168	3.6 ± 1.5	2.0 ± 0.5	1.5 ± 0.3		
9	48	192	1.5 ± 0.9	1.0 ± 0.3	0.6 ± 0.1		
10	72	216	0.8 ± 0.4				

* Average concentrations, together with their standard deviations, are expressed in milligrams per 100 cc. of whole blood.

† These hours refer to the time at which the blood samples were taken, in relation to each daily maintenance dose.

‡ These hours refer to the total elapsed time following the initial dose.

The data obtained following the administration of sulfamethazine, sulfathiazole, and sulfadiazine are presented graphically in Figure 1, together with the curve for the same dose of sulfamerazine. The concentration in the blood 2 hours following the initial dose of sulfamethazine equaled that produced by sulfamerazine. However, the concentration of sulfamethazine decreased rapidly, whereas the concentration of sulfamerazine rose slightly during the next 2 hours and then decreased gradually to a level, 24 hours after dosage, of more than twice that of sulfamethazine. The concentration of sulfathiazole, although higher than that of sulfadiazine during the first 6 hours, was lower thereafter, and markedly lower than that of both sulfamethazine and sulfamerazine during the entire 24-hour period.

Attention is directed particularly to the curves in Figure 1, relating to the *last* day of dosage, which day was typical of all days on maintenance dosage (Table 1). The concentration of sulfadiazine was consistently higher than that produced by sulfathiazole in equal dosage, and, except for the 4-hour period following each maintenance dose, was greater than that of sulfamethazine. However, on the same dosage, sulfamerazine maintained a concentration in the blood approximately twice that of sulfadiazine, and several times that of sulfathiazole.

In Figure 2 curves are presented which facilitate comparison of the concentrations of sulfonamide in the blood produced by the dosages of

sulfamerazine and sulfadiazine employed. The greater efficiency of sulfamerazine, in comparison with sulfadiazine, in producing and maintaining sulfonamide concentrations in the blood is shown. Thus, with an initial 2 gm. dose of sulfamerazine, followed by daily maintenance doses of 1 gm., the average daily concentration of free sulfamerazine in the blood of these subjects decreased from a peak of about 6.5 mg. to a low of 3.5 mg. per 100 cc. Following an initial dose of 1 gm. and daily maintenance doses of 0.5 gm., the average maximal blood level with sulfamerazine was about 4 mg. and the minimal about 2 mg. per 100 cc. When an initial 2 gm. dose of sulfadiazine was given, followed by 1 gm. daily, the concentration in the blood rose each day to about 3.5 mg. and fell to about 1.5 mg. per 100 cc.

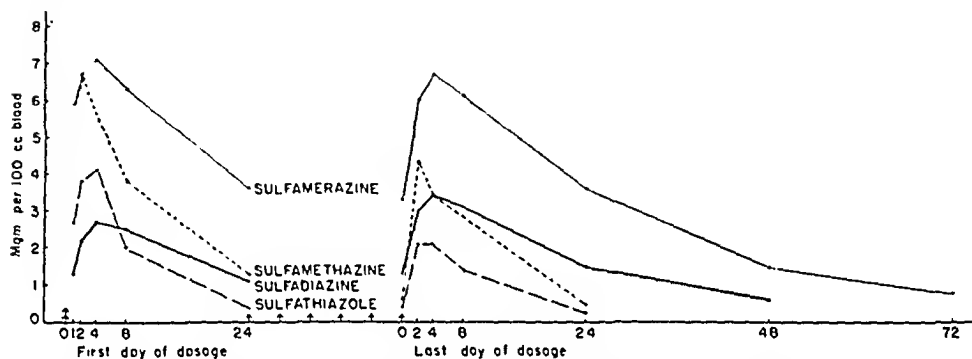


FIG. 1.—The average free sulfonamide concentration in the blood of 8 normal men following the oral administration of sulfamerazine, sulfamethazine, sulfadiazine and of sulfathiazole; an initial dose of 2 gm. of each drug was given followed by a maintenance dose of 1 gm. daily for a total period of 6 or 7 days.

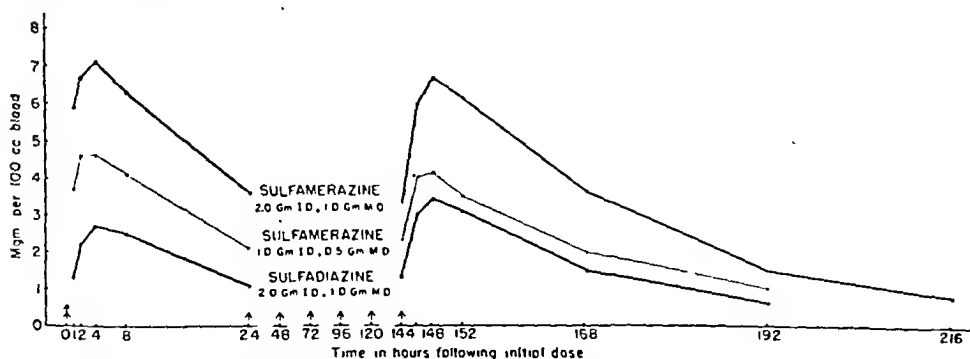


FIG. 2.—The average free sulfonamide concentration in the blood of 8 normal men following the oral administration of sulfamerazine and of sulfadiazine once daily for a period of 7 days. The blood levels shown are those resulting from the first and last days of dosage. (I.D. = initial dose; M.D. = maintenance dose.)

These data indicate that the dosage of sulfamerazine necessary to maintain any reasonable concentration of sulfonamide in the blood should be significantly less than that required with each of the other 3 drugs.

No significant effects of the sulfonamides on the average total leukocyte counts were seen, although 2 individuals consistently showed decreased counts following each exposure to a sulfonamide.

Data on the renal elimination of the 4 sulfonamides are presented in Table 2. From these data it is apparent that the percentages of conjugated sulfonamide which appeared in the urine were less with sulfadiazine and sulfathiazole than with either sulfamerazine or sulfamethazine. The greatest percentage of conjugated drug was excreted following sulfamethazine administration. It will be noted (Table 2) that the average percentage of conjugated sulfonamide found in the urine following the administration of a given drug was very constant. These data reflect the remarkable constancy with which each individual conjugated each sulfonamide.

TABLE 2.—AVERAGE SULFONAMIDE CONTENT OF THE URINE, COLLECTED DURING 24-HOUR PERIODS, OF MEN RECEIVING SMALL MAINTENANCE DOSES OF VARIOUS SULFONAMIDES

Drug	Daily maintenance dose (gm.)	Day of dosage	Average amount of free sulfonamide (gm.)	Average amount of conjugated sulfonamide (gm.)	Conjugated sulfonamide (%)
Sulfamerazine . .	0.5	6	0.21 \pm 0.06	0.29 \pm 0.05	57.4 \pm 11.1
	1.0	5	0.35 \pm 0.11	0.50 \pm 0.11	58.8 \pm 12.4
	1.0	7	0.40 \pm 0.13	0.50 \pm 0.12	55.7 \pm 12.5
Sulfadiazine . .	1.0	5	0.50 \pm 0.09	0.25 \pm 0.07	33.8 \pm 6.0
	1.0	7	0.59 \pm 0.11	0.26 \pm 0.05	30.5 \pm 5.4
Sulfamethazine . .	1.0	5	0.28 \pm 0.15	0.64 \pm 0.17	70.0 \pm 14.0
	1.0	6	0.28 \pm 0.16	0.64 \pm 0.16	69.7 \pm 17.0
Sulfathiazole . .	1.0	5	0.63 \pm 0.10	0.27 \pm 0.10	27.1 \pm 7.3
	1.0	6	0.70 \pm 0.10	0.25 \pm 0.10	26.3 \pm 5.7

Comment.—The data on renal elimination and concentration in the blood confirm our previous findings²¹ in which the absorption of sulfamerazine was shown to be more rapid and more complete, and the excretion by the kidney slower, than that of sulfadiazine. These findings account for the maintenance of a given concentration in the blood with smaller doses of sulfamerazine than with sulfadiazine.

Although with small doses, such as were given in this study, urinary solubility is not a particularly important factor, it may be well to comment on the relative solubilities of these drugs, particularly on the relation between sulfadiazine and sulfamerazine. Gilligan *et al.*^{8,9} emphasize the great importance, in the prevention of renal complications, of the maintenance of a neutral or alkaline urine, which enormously increases the solubility of sulfadiazine, sulfamerazine and sulfamethazine, and their acetyl derivatives. In contrast, as is shown in their Table 4, the solubility of sulfapyridine, acetylsulfapyridine or of acetylsulfathiazole is very little increased by alkalization. The absolute solubilities of sulfadiazine, sulfamerazine and their N₄-acetyl derivatives were found to be somewhat greater in urine²¹ than in buffered solutions.^{8,9} The solubilities of sulfamerazine and acetylsulfamerazine were somewhat greater than those of sulfadiazine and acetylsulfadiazine, respectively, in urine at acid pH levels. This is of importance since it is at acid pH levels that there is danger of precipitation of the drugs in the urinary tract. Also of significance is the fact that in maintaining a given blood level, larger doses of sulfadiazine, sulfamethazine or sulfathiazole are required than of sulfamerazine and,

therefore, the total amount of drug which must pass through the kidneys each day is appreciably less with sulfamerazine than with any of the other sulfonamides.

The maintenance of equivalent sulfonamide concentrations in the blood, by the administration of sulfamerazine in doses one-half as large as those of sulfadiazine, leads to the appearance in the urine of closely similar amounts of the acetylated derivatives (Table 2). Under these circumstances, however, the danger of crystal formation is appreciably less with sulfamerazine than with sulfadiazine because of the greater solubility of acetylsulfamerazine in urine of normal acidity. Care should of course be taken, when either these or other sulfonamides are used, to prevent the excretion of urine of low volume or of low pH, conditions which favor precipitation in the urinary tract of the acetylated derivatives of all the sulfonamides now available.

The concentration produced in the blood by single daily doses of 0.5 or 1 gm. of sulfamerazine should be of clinical significance. Several investigators have described beneficial effects from the use of small doses of sulfanilamide, given over long periods, in the prophylaxis of streptococcal infection in rheumatic subjects.^{2,4,13,14,18,19}

Loveless and Denton¹⁶ used sulfathiazole in the prophylaxis of gonorrhea. The drug was given in doses of 2 gm. to soldiers leaving a post, and, if "station prophylaxis" were not given, an additional 2 gm. was administered on return to camp and 2 gm. the following morning. Unfortunately blood level data were not given. The authors found a marked reduction in the incidence of gonorrhea and of chancroid in the group treated as described, in comparison with a large group of soldiers to whom sulfonamides were not administered.

Recently Watson *et al.*²⁰ presented convincing evidence of the control of a scarlet fever epidemic, in which several thousand men were given repeated daily 1 gm. doses of sulfadiazine, and among whom only 3 developed any sign of toxicity (rash). In a group of 50 of these men the average and median sulfadiazine concentration, about 6 hours following dosage, was 2.6 mg. per 100 cc. of blood. This agrees well with our observations, made in a smaller group, but at a comparable time and with the same dose, which indicated the presence of about 3.2 mg. of sulfadiazine per 100 cc. of blood. It should be noted that the daily administration of sulfamerazine in doses of only 0.5 gm. results in the maintenance of an average concentration of free sulfonamide in the blood higher than is produced by daily 1 gm. doses of sulfadiazine, sulfamethazine or sulfathiazole.

Sulfamerazine is so rapidly absorbed and slowly excreted, in comparison with other sulfonamides, that smaller daily doses should be given, and at less frequent intervals, in order to maintain adequate prophylactic or therapeutic blood levels. Clinical findings indicate that a total daily dose of 1 gm. to 4 gm. of sulfamerazine may be given on the basis of only 2 or 3, instead of the customary 4 to 6, divided doses daily.

Summary.—The average sulfonamide concentrations produced in the blood of 8 normal men by daily 1 gm. doses of sulfamerazine, sulfadiazine, sulfamethazine and sulfathiazole are presented (Fig. 1). The concentration in the blood following maintenance doses of sulfamerazine fell from a daily maximal value of about 6.5 to a minimal value of about 3.5 mg. per 100 cc.; with sulfadiazine from about 3.5 to about 1.5; with sulfamethazine from about 4 to less than 1; and with sulfathiazole from about 2 to less than 1 mg. per 100 cc. Sulfamerazine administered in single 0.5 gm. daily doses (Fig. 2) maintained a concentration in the blood which fell gradually from a level of approximately 4 to a level of about 2 mg. per 100 cc.

Emphasis is placed on the rapid absorption and gradual elimination of sulfamerazine, which make possible the maintenance of a concentration in the blood, with single daily doses of only 0.5 to 1 gm., that is probably sufficient for certain chemoprophylactic purposes. The data presented, as well as clinical experience with sulfamerazine, indicate that adequate therapeutic concentrations in the blood should be maintained by the administration of smaller total daily doses than with other sulfonamides; these doses can be given on the basis of only 2 or 3 divided doses daily.

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STUDIES ON BONE MARROW IN VITRO

II. THE EFFECT OF HEMOGLOBIN AND RED CELL STROMATA ON EXPLANTED BONE MARROW

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IN a previous paper⁵ we have reported experiments on rabbits' bone marrow surviving *in vitro*. The fundamental physiologic activities of the organ, such as maturation of the white and red cells and multiplication of their precursors, taking place during the first days of incubation, were described.

After establishing the behavior of the explanted bone marrow in standard medium, the direct effect of certain substances on the surviving and functioning bone marrow was investigated. The cellular composition of the bone marrow surviving in media containing the added respective substances was studied and compared with that of the bone marrow surviving in standard medium.

This report deals with the effect of hemoglobin solutions and suspensions of red cell stromata on the bone marrow surviving *in vitro*.

Material and Methods. The description of the method to maintain bone marrow fragments *in vitro* is given in the first paper of this series.⁵

Solutions of hemoglobin and suspensions of red cell stromata were obtained in the following way: 10 cc. of rabbits' heparinized blood were centrifuged, the plasma withdrawn, and the remaining red cells washed twice with Ringer solution. Then distilled water was added in the proportion 4 to 1 until the solution had become laked. After further centrifugation, a pure supernatant hemoglobin solution was obtained. The sediment, consisting of red cell stromata, was washed several times with Ringer's solution and, after pouring off the supernatant fluid, a volume of Tyrode solution, equal to the sediment, was added and a suspension of stromata was obtained.

One drop of hemoglobin solution, or one drop of the stroma suspension was added to each tube containing the standard medium (3 drops of Tyrode solution, 3 drops of heparinized rabbits' plasma and 1 drop of chick embryonic extract).

A set of 18 tubes was used in each experiment, so that 6 control tubes contained the bone marrow in the standard medium, 6 the added hemoglobin solution and 6 the added suspension of red cell stromata. Altogether, 9 such experiments on bone marrow obtained from 9 rabbits of the age of approximately 6 to 8 weeks were performed. The bone marrow fragments were incubated for 24 hours and 48 hours and were then histologically examined. After fixation in Zenker's fluid the specimens were embedded in celloidin paraffin. Serial sections 4 μ thick were made and stained with hematoxylin-eosin and with Giemsa's stain.

Results. *Effect of Hemoglobin Solution on Bone Marrow in Vitro.* After an incubation period of 24 and 48 hours the bone marrow sur-

* Working under the Cancer Laboratories fellowship.

living *in vitro* in a medium to which hemoglobin solution was added, is well preserved and without signs of degeneration. The surrounding plasma coagulum contains a varying number of polymorphonuclear leukocytes which have migrated from the explant. The explant itself

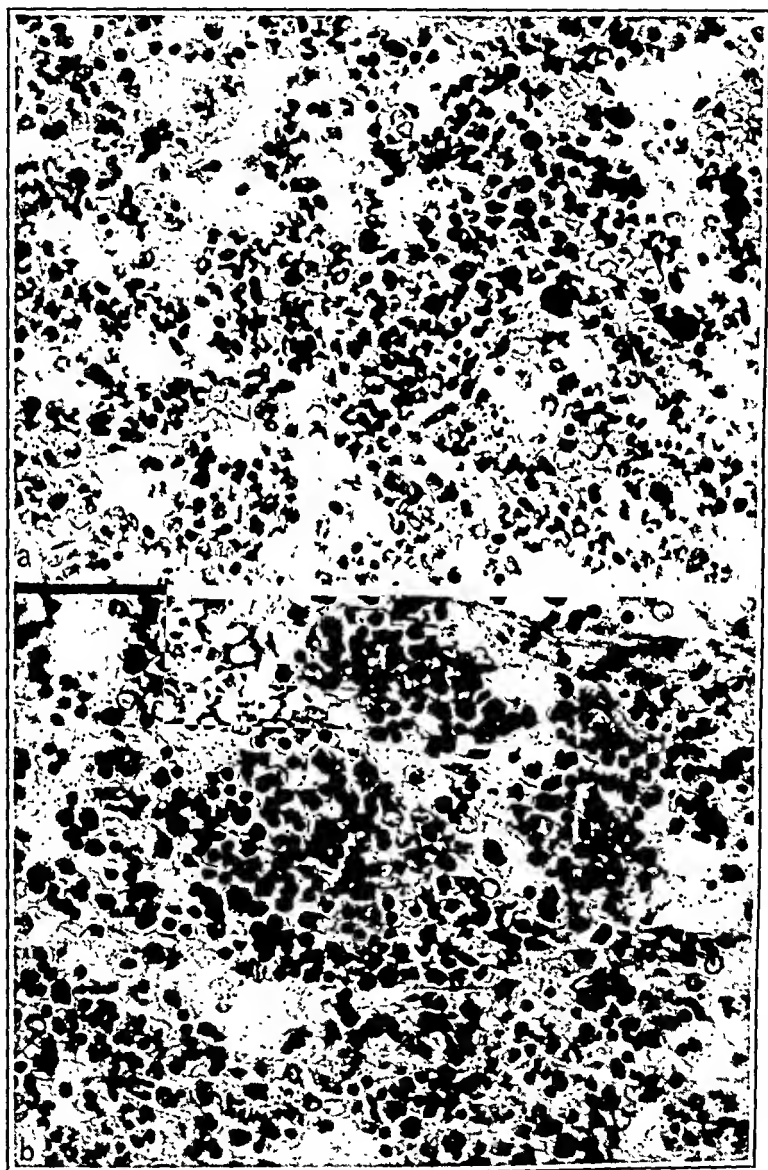


FIG. 1.—Experiment K. 29. Mag. $\times 500$. Hematoxylin-eosin. *a*, Explant of bone marrow in hemoglobin containing medium after 24 hours of incubation. *b*, Explant of bone marrow in stroma containing medium after 24 hours of incubation.

is exceedingly rich in myeloid and erythroid cells. A close inspection reveals an abundance of polymorphonuclear leukocytes which, particularly in the central parts of the fragment, densely fill the trabeculae and are aggregated in large groups; between them numerous red cells

are also to be found (Figs. 1a, 2a, 3a). Stem cells, myelocytes and nucleated red cells are scattered throughout the central parts of the fragment, and are more concentrated in the peripheral zones. Here numerous immature cells in mitotic division are to be seen.



FIG. 2.—Experiment K. 28. Mag. $\times 500$. Hematoxylin-eosin. a, Explant of bone marrow in hemoglobin containing medium after 24 hours of incubation. b, Explant of bone marrow in stroma containing medium after 24 hours of incubation.

Analyzing the effect of hemoglobin-containing medium on the bone marrow surviving *in vitro*, it is important to remember that, as we have demonstrated in our first paper, the bone marrow culture in the standard medium showed definite signs of maturation and contained a larger number of polymorphonuclear leukocytes and erythrocytes than

the fresh material. Comparison between the explants in hemoglobin-containing medium and those in standard medium after 24 hours of incubation reveals the following results:

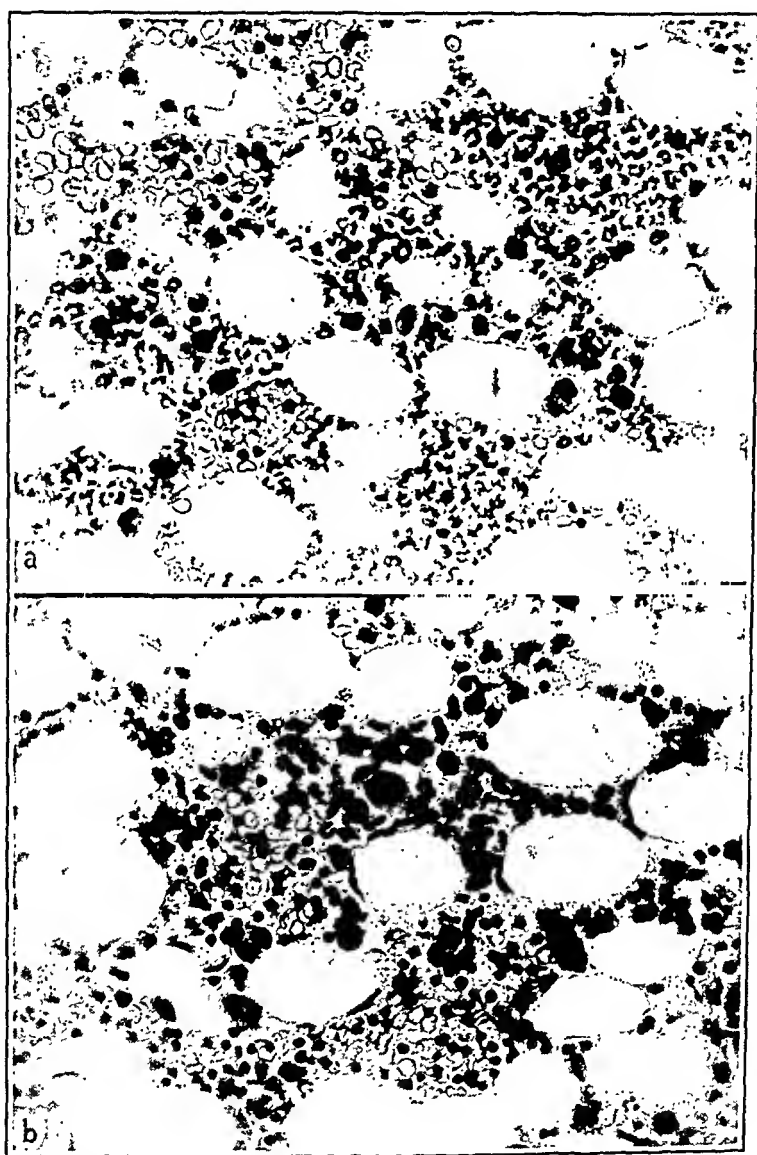


FIG. 3.—Experiment K. 24. Mag. $\times 500$. Hematoxylin-eosin. *a*, Explant of bone marrow in hemoglobin containing medium after 24 hours of incubation. *b*, Explant of bone marrow in stroma containing medium after 24 hours of incubation

The number of polymorphonuclear leukocytes in the explants in hemoglobin-containing medium was in most experiments higher than in the explants in standard medium. The abundance of leukocytes in the experimental fragments was particularly striking in cultures deriving from bone marrow with prevailing leukopoietic activity. In the few experiments on bone marrow with prevailing erythropoietic

activity, the number of leukocytes was low, but relatively higher than in the control fragments. In these instances the predominant cell type were mature red cells.

In order to establish the relationship of the various cell elements in the control and in the experimental bone marrow explants respectively, differential cell counts were made of mature and immature white cells as well as nucleated red cells present in the bone marrow fragments incubated in standard medium and in hemoglobin-containing medium.

TABLE 1.—PERCENTILE INCREASE OF POLYMORPHONUCLEAR LEUKOCYTES IN EXPERIMENTAL FRAGMENTS AS COMPARED WITH CONTROLS

Animal No.		No. of cells counted	Stem cells (%)	Myelocytes (%)	Polymorphonuclear leukocytes (%)	Nucleated red cells	Myeloid: erythroid ratio
R. 24	A	816	1.0	21.3	39.1	38.6	1.6:1
	B	900	0.4	20.9	38.9	39.8	1.5:1
	C	1061	1.8	23.6	18.9	55.7	0.8:1
R. 27	A	815	28.9		42.7	28.4	2.5:1
	B	1299	23.3		49.4	27.3	2.7:1
	C	940	31.7		12.1	56.2	0.8:1
R. 28	A	1584	1.3	10.4	40.7	47.6	1.1:1
	B	1736	1.2	14.4	43.0	41.4	1.4:1
	C	1468	1.7	13.3	15.5	69.5	0.4:1
R. 29	A	873	1.0	20.3	40.2	38.5	1.6:1
	B	1467	0.3	13.1	43.9	42.7	1.3:1
	C	1205	1.1	7.9	24.7	66.3	0.5:1
R. 30	A	1367	20.5		32.5	47.0	1.1:1
	B	1430	14.8		37.9	47.3	1.1:1
	C	1130	20.1		18.0	61.9	0.6:1
R. 32	A	1162	24.1		20.1	55.8	0.8:1
	B	1356	17.5		35.2	47.3	1.1:1
	C	531	18.1		13.9	68.0	0.5:1
R. 33	A	793	18.8		17.4	63.8	0.6:1
	B	946	13.3		25.3	61.4	0.6:1
	C	ca.900	17.3		15.9	66.8	0.5:1
R. 34	A	926	17.9		16.8	65.3	0.5:1
	B	767	17.9		17.7	64.4	0.6:1
	C	576	21.5		12.5	66.0	0.5:1
R. 35	A	591	22.3		26.9	50.8	1.0:1
	B	701	16.5		43.7	39.8	1.5:1
	C	728	17.2		30.1	52.7	0.9:1

A = Section of 24 hours old explants in standard medium.

B = Section of 24 hours old explants in standard medium with addition of hemoglobin solution.

C = Section of 24 hours old explants in standard medium with addition of stroma suspension.

Table 1 shows that there was a marked percentile increase of polymorphonuclear leukocytes in the experimental fragments as compared with the controls, in 6 out of 9 experiments, the average increase being 9.3%. In 1 case they were only slightly increased, in 2 cases the number of polymorphonuclear leukocytes remained the same. The relative

increase of the polymorphonuclear leukocytes was usually higher when originally the absolute number of leukocytes was low.

A corresponding percentile decrease of stem cells and myelocytes in the experimental fragments compared with the control fragments was found in 6 out of 9 experiments. In 2 cases in which the number of polymorphonuclear leukocytes in the experimental fragments remained the same as in the control fragments, the number of stem cells and myelocytes was also the same, and in 1 case there was a slight increase in the experimental fragments.

The percentage of nucleated red cells was practically the same in the experimental as in the control fragments in 4 out of 9 cases. In 4 cases the experimental fragments contained a somewhat lesser number of nucleated red cells, and in 1 case there was a slight increase in the experimental fragments.

Table 1 shows also that the myeloid-erythroid ratio in the experimental fragments remained the same as in the control fragments in 5 out of 9 experiments, was shifted in favor of the myeloid elements in 3 cases, and was only slightly shifted in favor of the erythroid elements in 1 case.

The results of these counts indicate that the addition of hemoglobin produced an increased rate of maturation of polymorphonuclear leukocytes in most experiments as compared with the explants in standard medium. Apart from the increased maturation, multiplication evidenced by mitotic activity was also noted in the experimental fragments. The rate of multiplication, however, was usually somewhat less than in the control fragments. The number of mitoses counted in the respective bone marrow fragments is given in Table 2.

TABLE 2.—EFFECT OF RED CELL STROMATA ON BONE MARROW IN VITRO

Animal No.	No. of mitoses in 10 high-power fields	Animal No.	No. of mitoses in 10 high-power fields
R. 24	A 7	R. 35	A 7
	B 5		B 7
	C 9		C 13
R. 27	A 4	R. 32	A 12
	B 5		B 7
	C 10		C 10
R. 28	A 8	R. 33	A 5
	B 6		B 3
	C 14		C 6
R. 29	A 17	R. 34	A 9
	B 11		B 10
	C 19		C 12
R. 30	A 12		
	B 11		
	C 11		

A = Section of 24 hours old explant in standard medium.

B = Section of 24 hours old explant in standard medium with addition of hemoglobin solution.

C = Section of 24 hours old explant in standard medium with addition of stroma suspension.

Effect of Red Cell Stromata on Bone Marrow in vitro. The bone marrow explants in media to which a suspension of red cell stromata was added, exhibit quite a different picture than the explants in hemoglobin-containing and in standard medium. The outstanding feature of these explants after 24 hours of incubation is the scarcity of polymorphonuclear leukocytes. A further characteristic of the stroma-containing cultures is the prevalence of immature cells, particularly of the red variety.

Erythroblasts, normoblasts, and in a lesser degree stem cells, and myelocytes, fill the stroma meshes throughout the entire pieces (Figs. 1b, 2b, 3b). Besides there are numerous erythrocytes sometimes accumulated in certain regions and forming lakes.

Another typical feature of these cultures is the particularly high number of mitoses in the precursors.

The comparison of the bone marrow pattern of fragments in stroma-containing medium with that of fragments in standard medium reveals the constant and definite reduction of the number of polymorphonuclear leukocytes in the experimental fragments compared with the control fragments. This difference was particularly striking in experiments on bone marrow with prevailing leukopoietic activity, but also seen to a lesser degree in the experiments on bone marrow with prevailing erythropoietic activity.

With the reduction of the polymorphonuclear leukocytes a marked increase of the nucleated red cells in the experimental fragments was noted, as compared with the control fragments.

The percentile numbers of the different cell types given in Table 1 show the changes which have taken place in the experimental fragments in comparison with the control fragments.

Table 1 shows that there is a reduction of polymorphonuclear leukocytes in the experimental fragments as compared with the control fragments in 7 out of 9 experiments, the average reduction being 16.9%. In 1 case they remained practically the same and in 1 case there was a slight increase in the experimental fragments. The percentage of nucleated red cells was clearly augmented in 6 out of 9 cases, the average increase being 20.3%. In the other 3 cases the increase was very small, reaching only an average of 1.9%. In 2 of these cases there was already an abundance of nucleated red cells in the control fragments, these deriving from erythropoietic bone marrow.

The number of stem cells and myelocytes was in 4 out of 9 cases slightly increased in the experimental fragments, in 2 cases practically the same as in the control fragments, and in 3 cases it was somewhat decreased.

It is clearly seen that in the experimental fragments the myeloid-erythroid ratio is definitely shifted in favor of the erythroid elements in 6 out of 9 cases in comparison with the control fragments. From the 3 cases where the myeloid-erythroid ratio remained unchanged, 2 cases were experiments on erythropoietic bone marrow in which the number of nucleated red cells was already very high in the original bone marrow.

Judging from the reduced number of polymorphonuclear leukocytes in the experimental fragments it must be concluded that the addition of red cell stromata rather inhibits white cell maturation. On the other hand, the prevalence of precursors indicates that an increased rate of multiplication has taken place. This is manifested by an increased number of mitoses in the experimental fragments which was found in 7 out of 9 experiments (Table 2).

Table 2 shows that the highest number of mitoses was counted in the fragments surviving in the stroma-containing medium.

Discussion. The effect of the individual components of the red cell on hemopoiesis was the subject of study of many investigators.

The direct effect of hemoglobin on bone marrow cultures was briefly described by Jeney,¹ who claimed to have observed a stimulating effect on hemopoiesis, manifested by an increased number of nucleated red cells. As far as we know, no experiments with the addition of red cell matrix to bone marrow cultures have been performed.

Experiments on animals concerning the effect of hemoglobin on the bone marrow have been registered by McMaster and Haessler² and by Miller and Rhoads.³ The former authors found an increase of the hematopoietic tissue and especially of the erythropoietic islands in bone marrow of rabbits rendered anemic by repeated bleedings in which the blood loss was replaced by injections of hemoglobin. Miller and Rhoads, using the same technique, found likewise erythroblastic hyperplasia, but with the appearance of megaloblasts in the bone marrow of the injected animals.

No data in the literature are available concerning the effect of the red cell stromata on the bone marrow *in vivo*.

The effect of injected hemoglobin on blood regeneration has been extensively studied by Whipple and co-workers.⁷ These authors found that, if a stroma-free solution of hemoglobin was administered intravenously or intraperitoneally to dogs rendered anemic by repeated bleedings, 80 to 90% of the hemoglobin injected was recovered in newly formed cells. Robschitz-Robbins⁶ assumed that hemoglobin breakdown products are direct irritants to the bone marrow as well as building stones.

The effect of red cell stromata on blood regeneration was investigated by Ono.⁴ According to this author the intravenous injection of red cell stromata in quantities corresponding approximately to the daily red cell destruction, produced an increase of hemopoiesis in rabbits.

The experiments described in this paper indicate that there is a distinct difference in the response of the bone marrow surviving *in vitro* to hemoglobin and red cell stroma. The addition of hemoglobin to the standard medium resulted in an increase in the number of mature cells. The effect of stroma, on the other hand, was characterized by an increased number of immature cells, mainly red cells precursors, and reduction of mature white cells. Both components of the erythrocyte had thus a stimulating effect on the bone marrow *in vitro*. The stimulation caused by hemoglobin was manifested mainly in the direction of maturation, while the effect of stroma was seen in the direction

of multiplication—particularly of the erythroid elements, thus producing *in vitro* an erythroblastic bone marrow.

Summary. A different and characteristic response of explanted bone marrow to both components of the erythrocyte was found.

The addition of hemoglobin resulted in an increased rate of maturation of white and red blood cells.

The addition of red cell stromata, on the other hand, produced an increased rate of multiplication, particularly of the red cell precursors.

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CARDIAC ARRHYTHMIAS IN 1000 CASES OF PULMONARY TUBERCULOSIS

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THE evaluation of the clinical significance of cardiac arrhythmias encountered in cases of pulmonary disease requires the consideration of the anatomically adjacent extracardiac factors. Otherwise, their significance is that of arrhythmias in general. They very frequently occur in the absence of cardiac disease. At times, however, they constitute the sole evidence of severe myocardial embarrassment. Their presence in cases of pulmonary disease may be purely accidental. One is justified, however, in correlating their occurrence with existing extracardiac factors and in considering in some cases the probability of an etiologic dependence. Such consideration may give the existing arrhythmia a special function—that of an indicator that pathophysiologic activities originating in the pleuro-pulmonary apparatus have invaded the heart. The clinician, naturally, may be influenced in his prognosis and therapeutic approach by the consideration of this etiologic dependence.

In cases of pulmonary tuberculosis the extracardiac factors in the causation of abnormal cardiac rhythm may be one or a combination of several of the following: (1) The influence of the tuberculous process on the intravascular pulmonary tension. (2) The anatomic involvement of the pericardium and myocardium in the process consuming the adjacent pulmonary tissue. (3) The toxic influence of the disease on the heart muscle and the conduction system. (4) The mechanical

involvement of the heart and the great vessels in mediastinal torsion and displacement. (5) Reflexes initiated in the disturbed anatomy and physiology of the respiratory apparatus without the mechanical involvement of the heart and great vessels.

An attempt to evaluate some of these factors is the purpose of the present report.

Material and Results.—The electrocardiograms of 1000 consecutive cases with evidence of chest tuberculosis admitted to Sea View Hospital were reviewed with particular reference to the incidence and type of arrhythmias encountered. There were 78 cases presenting arrhythmias (Table 1). Twelve cases showed sinus arrhythmia; 22 presented premature auricular contractions and premature ventricular contractions; 14 cases presented various types of auriculoventricular conduction impairment, mostly first stage heart block; 20 cases presented intraventricular conduction impairment; 10 cases presented miscellaneous arrhythmias which included: sinus block, 1 case; sinus arrhythmia with paroxysmal nodal rhythm, 1 case; sinus bradycardia, 1 case; auricular fibrillation, 3 cases; auricular tachycardia, 2 cases; auricular flutter, 1 case; premature auricular and ventricular contractions with paroxysmal auricular tachycardia, 1 case.

TABLE 1.—TYPE OF ARRHYTHMIA IN RELATION TO AGE AND CARDIAC DISEASE

	Age (yrs.)			Cardiac disease	
	15 to 49 (incl.)	50 and over	Total	Present	Absent
Arrhythmia:					
Sinus arrhythmia	11	1	12	1	11
Premature contractions	11	11	22	13	9
Delayed auriculoventricular con- duction time	10	4	14	11	3
Delayed intraventricular conduc- tion time	6	14	20	19	1
Miscellaneous	3	7	10	9	1
Total				53	25

The cases with intraventricular conduction impairment were included, as they frequently are, in the classification of cardiac arrhythmias, although, strictly speaking, they are rhythmic arrhythmias.

When the arrhythmias were tabulated in relation to the activity of the pulmonary process (Table 2) as evidenced by positive sputum, elevated temperature, and increased sedimentation rate, it was noted that there were 4 times as many cases of arrhythmias in the active group as in the inactive group. However, the observation is without significance, as the Sea View Hospital population is made up of about 4 times as many active as inactive cases.

When the arrhythmias are tabulated in relation to the site, type, and extent of the pulmonary lesions (Table 3), a fact which may have some significance becomes prominent, namely, that arrhythmias are more frequently associated with right-sided than with left-sided lesions. The great vessels and nerve structures are more exposed on the right side than on the left; possibly their distortion is at least reflexly responsible for the abnormal cardiac manifestations.

Table 1 presents the arrhythmias in relation to age and cardiac disease. With one exception the sinus arrhythmias occurred in the younger age group, and with one exception no evidence of cardiac disease was obtained in this arrhythmia group. Premature contractions were equally divided between the 2 age groups. The majority of them had evidences of cardiac disease. The miscellaneous arrhythmias had evidences of cardiac disease in all but one case, and the majority of them occurred in the older age group. The intraventricular and the auriculoventricular conduction impairment group was also predominantly associated with evidences of cardiac disease.

The evidence of cardiac disease consisted of objective criteria, namely, a history of syphilis or polyarticular rheumatism; physical findings such as peripheral sclerosis or unmistakable cardiac murmurs indicative of mitral or aortic disease; fluoroscopic and Roentgen ray evidences of enlargement of the heart and aorta; and typical electrocardiographic changes indicative of coronary artery occlusion.

Comment.—We are not aware of any statistical information on cardiac arrhythmias comparable with the type of material in Sea View Hospital. This institution is one of the few places in the United States where routine electrocardiograms are taken on admission of every case. The statistics available, such as those of White and Jones,⁵ are based on electrocardiograms taken of patients with cardiac symptoms. To compare our figures with this group will not be instructive.

To the best of our knowledge there is only one fairly large series of cases of pulmonary tuberculosis with electrocardiographic studies reported, the one by Leverton.³ While this author does not specifically discuss cardiac arrhythmias, he observed intraventricular impairment in 7.2% of his cases as compared with our 2%. The average age of his group was 39.4 years and only 6 out of 30 cases had clinical or post-mortem evidence of coronary sclerosis. It is his opinion that a nutritional disturbance of the myocardium occurs in pulmonary tuberculosis of long standing which may produce an electrocardiographic picture similar to that found in coronary sclerosis. Apparently, this contention is not borne out by our findings. Our study seems to indicate that the abnormalities in question are a manifestation of intrinsic cardiac disease and are related to the age group with vascular degenerative changes.

TABLE 2.—RELATION OF ARRHYTHMIA TO ACTIVITY OF TUBERCULOSIS

Arrhythmia:	Inactive	Active	Total
Sinus arrhythmia	5	7	12
Premature contractions	2	20	22
Delayed auriculoventricular conduction time	3	11	14
Delayed intraventricular conduction time	4	16	20
Miscellaneous	2	8	10
Total	16	62	

Auriculoventricular block in our series occurred predominantly in the younger age group. In only 3 cases, however, were no evidences of cardiac involvement present, other than the abnormal electrocardio-

gram. Of these 3 cases, one was 48 years old, one 18 years old, and one 32 years old. All 3 had considerable mediastinal shift. There is a possibility that in some cases mediastinal displacement can alter the configuration of the P wave so as to make it measurably consistent with the picture of first stage heart block.² This may possibly explain such reports as the one by Pastore.⁴ He observed a considerable number of cases of auriculoventricular block in tubercular children without evidences of rheumatic fever. However, it is possible that in a small number of cases toxic influences of the tuberculous process may also play a rôle in the causation of conduction difficulties.

TABLE 3.—ARRHYTHMIAS IN RELATION TO PULMONARY LESIONS

	Type of arrhythmia					Total
	Sinus arrhythmia	Premature contractions	Delayed auriculo-ventricular conduction time	Delayed intra-ventricular conduction time	Miscellaneous	
Number of cases	12	22	14	20	10	78
Intrathoracic lesions	1	1	0	1	0	3
Exudative productive lesions:						
Unilateral (right)	1	0	1	1	0	3
Unilateral (left)	0	0	0	1	0	1
Bilateral:						
Predominant on right	1	0	0	0	1	2
Predominant on left	2	0	0	0	0	2
Caseous pneumonic lesions:						
Unilateral (right)	2	3	1	3	0	9
Unilateral (left)	0	0	0	0	0	0
Bilateral:						
Predominant on right	1	9	2	4	4	20
Predominant on left	3	4	3	1	1	12
Fibrotic lesions:						
Unilateral (right)	0	0	0	0	1	1
Unilateral (left)	0	0	0	0	0	0
Bilateral:						
Predominant on right	0	1	1	3	0	5
Predominant on left	0	0	2	0	0	2
Lesions equal bilaterally	1	4	4	6	3	18
Predominant lesions:						
Right	5	13	5	11	5	39
Left	5	4	5	2	2	18
Tracheal and mediastinal displacement:						
Right	6	6	7	11		34
Left	0	2	2	1	2	7
Effusion pneumothorax hydro-pnx.:						
Right	3	3	2	6	3	17
Left	4	4	3	2	1	14

The effect of mediastinal displacement on the irritability of the myocardium has been stressed by a number of foreign writers and in this country by Brumfiel.¹ Of the 15 cases of mediastinal distortion studied by Brumfiel, 7 presented extrasystoles. While it is possible that a large number of the 1000 cases we studied had extrasystoles at some time, only 2.2% (22 cases) had premature contractions recorded in their admission electrocardiograms. Of these, 13 had evidences of intrinsic cardiac disease, and only 9 cases presented no such evidence, an incidence of about 1% in the entire group studied. This incidence is hardly significant when compared with the frequency of mediastinal

distortion seen at Sea View Hospital, as evidenced by Roentgen ray findings and the electrocardiographic abnormalities expressed in the directional changes of the QRS complex and T wave.

While the evidence points to the presence of intrinsic cardiac disease as an etiologic factor in producing arrhythmias, the findings in Table 3 are suggestive that extracardiac factors may play a rôle in precipitating the appearance of such arrhythmias. It is conceivable that in cases with mediastinal torsion the relationship and course of the cardiac nerves are likewise disturbed, and this may be responsible for the increased irritability of the myocardium. The structural arrangement of the right mediastinum may possibly supply the anatomic basis for the pathophysiologic changes. The predominance of right-sided lesions in the arrhythmia group is apparently not a reflection of case distribution in general. Out of 300 consecutive admissions reviewed with particular reference to this point, the number of cases with predominant right-sided lesions was about equal to the number of cases with predominant lesions on the left side.

Conclusion.—1. Pulmonary tuberculosis does not affect the incidence of abnormal cardiac rhythm or abnormalities in the conduction mechanism. In the majority of cases presenting these abnormalities, other clinical or laboratory evidence of intrinsic cardiovascular involvement can be elicited.

2. It is suggested that right pulmonary lesions involving the mediastinum may constitute an extracardiac factor in the causation of arrhythmias and conduction abnormalities in a *previously* diseased myocardium.

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THE SIGNIFICANCE OF MARKED LEFT AXIS DEVIATION OF THE ELECTROCARDIOGRAM*

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WHILE it is generally recognized that moderate deviation of the electrical axis of the heart to the left is a common finding in normal individuals, its frequency approximating 20%, there appears to be

* This paper is based on work carried out in 1937-38 at the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

little agreement as to the significance of the less frequent but by no means rare pattern of marked left axis deviation in which S_2 is of greater amplitude than R_2 (Fig. 1). References to this electrocardiographic pattern are few and opinions as to its significance are contradictory. Cohn¹ reported finding it once in a series of 218 normal soldiers.

Katz³ interprets this type of record as definitely abnormal, indicating left ventricular preponderance. Master⁴ has published a record of this type in a woman of 75 and described it as follows: "The electrocardiogram indicates the left ventricular hypertrophy by left axis deviation. It is otherwise normal." However, on the opposite page referring to

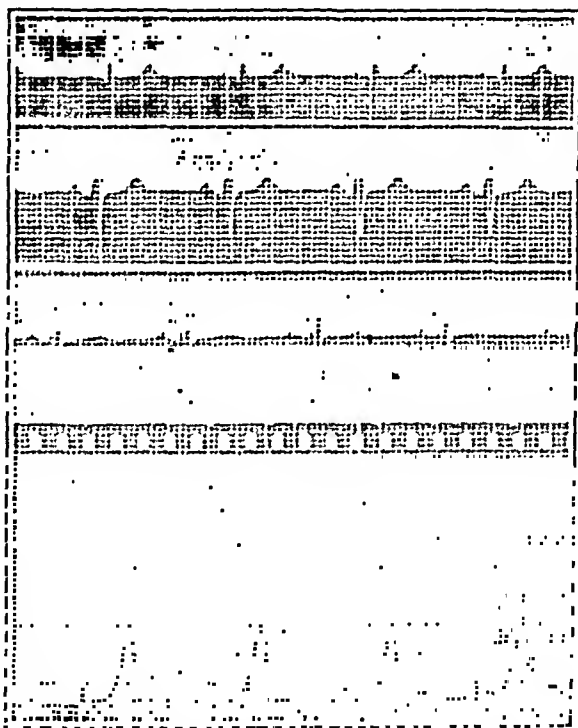


FIG. 1.—Pattern of marked left axis deviation.

the same record, he writes: "Electrocardiogram is negative. The left axis deviation is normal at this age." In the absence of any large scale study of the clinical and pathologic findings associated with the pattern under discussion it has been difficult to form an opinion as to its meaning.

In order to assess the significance of marked left axis deviation the clinical records of 200 consecutive cases exhibiting the pattern were studied. One hundred of these cases exhibited an upright T_3 and 100 exhibited an inverted T_3 .

To make a crude estimate of the relationship between predominant left-sided enlargement and the pattern under consideration, the cases were divided into 2 groups, based upon the clinical findings. In one

group were placed all the cases in which factors were present which might be expected to produce left ventricular enlargement—such as arterial hypertension or valvular disease. Hypertension was defined as a systolic blood pressure above 150 mg. Hg or a diastolic blood pressure above 90 mg. Hg. In this group were also included all cases exhibiting cardiac enlargement by Roentgen ray even if neither of the above etiologic factors were known to be present. In the second group were placed all cases with normal blood pressures, without valvular disease or in which the total transverse diameter of the heart as measured by Roentgen ray was less than one-half of the internal diameter of the thorax. It is clear that the criteria employed would not accurately separate all the cases of left ventricular enlargement from those with normal hearts, but there would be some error in both directions which would cancel out to a certain extent in such a large group. These figures indicate that 103 cases (51.5%) showed no obvious cause for or (when measured) positive Roentgen ray evidence of enlargement of the heart.

Measurements of the heart were made from teleroentgenograms in 97 cases and in 35 cases (37%) the cardiothoracic ratio was less than 50%.

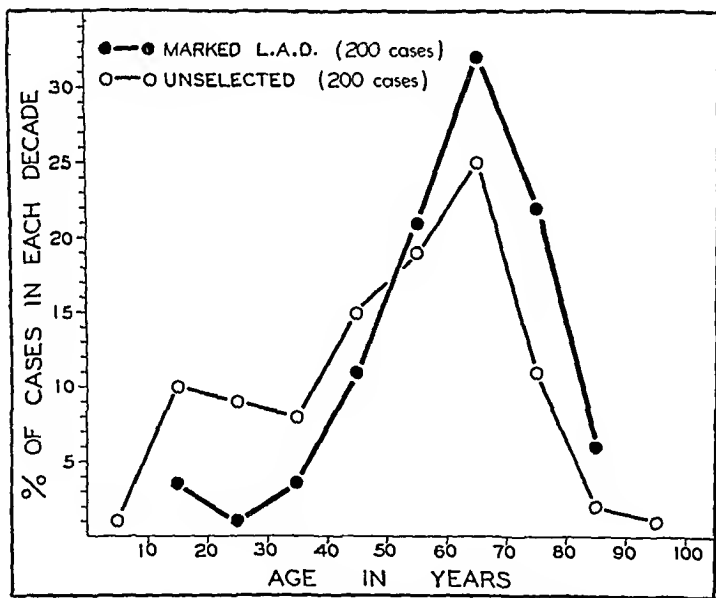


FIG. 2.—Age incidence of 200 cases exhibiting marked left axis deviation as compared to 200 unselected cases from the electrocardiographic laboratory. Note increased incidence in older decades.

A comparison of the age incidence of these 200 patients with marked left axis deviation with the age of 500 unselected cases from the electrocardiographic file showed a distinctly increased frequency of the condition in the older age groups (Fig. 2). A single chest lead (Lead IVF or IVR) was taken in each case and was normal in 186, abnormal in 14. These findings would suggest that the pattern of marked left axis deviation would not in itself alter the contour of the chest lead to an

abnormal degree such as is seen associated with the pattern of left ventricular enlargement.

The autopsy records of 27 cases were analyzed. The actual heart weights were as follows (italics indicate females): 700, 650, 640, 640, 600, 580, 540, 500, *500*, *465*, 450, 450, 420, 420, 420, *420*, *400*, 390, 340, 330, *310*, *310*, 300, 280, 275, 270, *250*. Ten of the hearts were of normal weight (below 400 gm. for men and 350 gm. for women). Coronary arteriosclerosis with slight or greater degrees of narrowing was present in 9 cases. One case exhibited complete occlusion of the descending branch of the left coronary artery with myocardial infarction. Myocardial fibrosis of greater or less degree was recorded in 12 cases and was absent in 13. It was not recorded in 2. Valvular disease was noted in 8 cases, 4 of aortic stenosis, 2 of aortic insufficiency and 2 of mitral stenosis.

Complete absence of any evidence of organic disease of the heart was recorded in 8 cases (30%).

Discussion. Deviation of the electrical axis to the left may be caused by any one of 4 factors, namely: 1. *Enlargement of the left ventricle.* In order to make a positive interpretation of left ventricular enlargement there must be certain changes in Lead I consisting primarily of a depression of the S-T interval and in more advanced cases by frank inversion of T₁, with concomitant changes in the opposite direction in Lead III. Not invariably present but of positive significance if found, is an increase in voltage of R₁. The actual deviation of the axis may be slight or, in vertically placed hearts, even absent. This pattern may develop even before there is detectable Roentgen ray evidence of enlargement.² Records of this type were excluded by the criteria employed.

2. *Delayed activation of the left ventricle,* easily recognized by the prolongation of the Q-S interval. Records of this type were also excluded by the criteria employed.

3. *Transverse position of the heart.* This is the most frequent cause of left axis deviation being found in individuals of stocky build or with high diaphragm from obesity, pregnancy, etc. It is due to rotation of the heart to the left on its A-P axis and may be recognized by a tendency to inversion of all the complexes in the third lead—P-waves and T-waves as well as the initial ventricular complex. Seldom if ever, does elevation of the diaphragm cause the marked degree of left axis deviation which is the object of this discussion. Although it was doubtless a contributing factor in some cases, the Roentgen ray studies did not reveal an abnormal frequency of transverse position of the heart in this series.

4. *Rotation of the heart to the right on its longitudinal axis.* This is the phenomenon which causes the paradoxical shift in the electrical axis to the left when a person lies on his right side. The effect of this rotation is to swing the left ventricle from a relatively posterior position in relation to the right ventricle into a position which is relatively less posterior and more lateral. Since the muscle mass of the left ventricle normally far exceeds that of the right ventricle, a slight degree of rota-

tion on the long axis would be expected to exert a marked effect on the electrical axis. This was clearly demonstrated on dogs by Meek and Wilson,⁵ who rotated the heart *in situ* by means of sutures attached to the epicardium. In man, rotation of the heart on its long axis might occur as the result of a congenital variation, a change in the shape of the thorax, displacement of the mediastinum by air, fluid or massive collapse of the lung, pleuro-pericardial adhesions, and by left ventricular enlargement. The degree of rotation necessary to produce a marked shift in electrical axis to the left may be so slight as to escape routine Roentgen ray or postmortem observation and it was not recorded in any of the cases in this series. In only a relatively small number of the cases were gross factors other than left ventricular enlargement noted which might explain rotation. The tendency of the axis to shift to the left with increasing age which has been described by Schlomka⁶ and confirmed by the present study could be ascribed to senile changes in the shape of the thorax with resultant rotation of the heart. In brief, the relationship of marked left axis deviation to rotation of the heart on its longitudinal axis remains a tenable but entirely unproved hypothesis, and whatever the explanation for this electrocardiographic variant may be, the fact stands out that a high percentage of the hearts which exhibit it are entirely normal in every respect. The figures are particularly significant because they come from a charity hospital where electrocardiograms are not taken as a routine but only if heart disease is suspected. In other words, this study is based on a group which has already been selected on the basis of suspected heart disease and which therefore is heavily weighted in that direction, so that the finding of as many as 30% *entirely* normal hearts at autopsy would indicate that marked left axis deviation is of no specific pathologic significance.

Summary. An attempt was made to correlate marked left axis deviation of the electrocardiogram with significant clinical and postmortem findings. A study of the clinical records in 200 cases revealed that 51.5% had no underlying reason for or evidence of, left ventricular enlargement.

Measurements of the heart from teleroentgenograms in 97 cases were within normal limits in 35 cases (37%).

In 27 autopsied cases the heart was entirely normal anatomically in 8 (30%). There was a definite increase in the incidence of the pattern in the older age groups.

Conclusion. The finding of marked left axis deviation in an otherwise normal electrocardiogram is to be regarded as a normal variation which, though encountered with increasing frequency with advancing age, cannot be correlated with ventricular enlargement, coronary disease or myocardial disease.

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DEVELOPMENT OF HYPERTENSION ASSOCIATED WITH LESIONS OF THE KIDNEY

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THE thought that renal disease is associated with an elevated blood pressure was initiated by Richard Bright more than a century ago. Subsequently, another interpretation of the cause for a rise of arterial tension was made by various clinicians in Germany, England, France, and the United States. Their ideas may be gathered from the terms they applied to hypertensive disease:

"Latent arteriosclerosis"—von Baseh 1876;

"Pre-albuminuric stage of Bright's disease"—Mahomed 1879;

"Pre-sclerosis"—Huchard 1893;

"Hyperpiesis"—Allbutt 1895;

"Essential hypertension"—Frank 1911;

"Hypertensive cardiovascular disease"—Janeway 1913;

"Malignant hypertension"—Keith, Wagner and Kernohan 1928.

A reversal of opinion came about in 1934 when Goldblatt and his colleagues published the results of their observations.² From their classical experiments which demonstrated that renal ischemia will cause a rise in blood pressure, they endeavored to establish a unitarian etiology for hypertension, namely, a functional derangement of kidney activity resting upon a morphologic basis.³

The efforts of Homer Smith,⁵ either through his own experiments or the application by others of methods devised by him, proved that in many cases of hypertension, not only is renal function normal but the flow of blood through the kidneys is not diminished. Definite evidence that hypertension is not necessarily secondary to renal disease was furnished by Castleman and Smithwick.¹ They investigated kidney biopsy material obtained at subtotal sympathectomy operations and discovered a considerable number of normal kidneys, both on gross inspection and on microscopic examination, in hypertensive patients. Thus the concept of primary, or essential, hypertension may be considered as definitely reestablished.

This does not imply that hypertensive states cannot be secondary to kidney disease. In chronic albuminuria due to nephritis, we have found that hypertension is more frequently developed as a serious complication than is renal insufficiency.⁴ Many reports have given enthusiastic accounts of cures of hypertension by unilateral nephrectomy. More recently, considerable skepticism on this score has arisen. Both urologists and pathologists have published a great deal of material showing that there are as many persons with lesions in the urinary tract who have hypertension, as persons without hypertension who have corresponding renal involvements. The climax of this situation is the conclusion of Homer Smith and his associates,⁵ that data from the literature are impressive in their statistical demonstration that unilateral renal disease and surgical lesions of the urinary tract do not predispose to hypertension.

The observation of a number of cases over a period of years, I believe, enables us to clarify this problem. It would appear that at the onset and during the earlier stages of any renal lesion there may be no rise in blood pressure, but as the involvement persists and progresses, there comes a time when intermittent elevations of blood pressure occur and, finally, the hypertension becomes permanently established. The reason for this is probably that both the pressor and antipressor substances generated by the diseased as well as the normal kidney, compensate for one another up to a certain point until those factors which increase the blood pressure dominate the picture, at first intermittently and, later, constantly. Numerous cases can be cited that demonstrate the individual phases of this whole series of events. However, one case that gives the complete picture furnishes satisfactory evidence, and is fairly conclusive in regard to the validity of these statements is represented by the data given in Table 1.

TABLE 1.—J. K., F., 31 (1935)

Date	Blood pressure	
	Systolic	Diastolic
1935 Feb. 25	176	104
June 22	152	94
July 23	136	94
1936 Feb. 25	156	94
1938 Oct. 17	164	94
29	164	104
1939 May 18	138	88
Oct. 31	154	94
1940 June 15	186	116
July 15	196	118
29	132	76
Oct. 4	162	96
26	142	94
1941 Jan. 4	176	106
16	202	126
18	172	98
Feb. 13	198	116
18	Right nephrectomy	
Apr. 3	134	88
June 4	142	86
July 11	136	86
Sept. 9	136	84
12	124	76
30	152	104
Oct. 1	114	76
1942 Jan. 3	132	82
Feb. 12	124	80
Apr. 14	118	82
July 17	128	80
Oct. 10	136	90
Dec. 29	132	88
1943 April 17	112	78
July 22	124	84
Sept. 25	136	86

Intermittent hypertension changing to persistent hypertension in 6 years. Return of blood pressure to normal after removal of an atrophic, functionless kidney caused by an aberrant vessel compressing the uretero-pelvic junction.

Case Study. This patient had a congenital obstruction at the right uretero-pelvic junction resulting from an aberrant vessel. From 1935, when she was 31 years old, to 1941, there was an intermittent rise in blood pressure to which

no detailed attention was paid largely because of the unwillingness of the patient to coöperate, and also for the reason that there were intervals when the blood pressure was at an approximately normal level. In 1941 the blood pressure became permanently elevated and it was at this time that a complete urologic examination was done; and a functionless right kidney demonstrated. Right nephrectomy showed that the kidney had been destroyed because of an aberrant vessel compressing the ureter at the uretero-pelvic junction. For a period of 2½ years following the nephrectomy the blood pressure dropped and remained at almost normal levels.

It is evident from these observations that a human being can carry a unilateral lesion in the kidney for 37 years, or perhaps longer before hypertension becomes permanent. The fact that the blood pressure maintained a much lower level for the observed period of 2½ years after the atrophic kidney had been removed, demonstrates that this diseased kidney had been responsible for the production of the elevated blood pressure.

Conclusions. Unilateral renal disease may exist for many years without affecting the blood pressure. As compensatory processes for the maintenance of normal arterial tension became strained, periods of intermittent rise in blood pressure occur. Finally, a permanent hypertension may develop. The extirpation of a unilaterally diseased kidney should prevent a rise in blood pressure, or remedy it if it has become permanently established, provided there are no causes for hypertension either in the remaining kidney or elsewhere in the body.

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STUDIES ON THE MORPHOLOGY OF THE ADRENAL CORTEX AND ON THE EXCRETION OF 17-KETOSTEROIDS IN HYPERTENSIVE PATIENTS

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It is well known that impaired function of the adrenal cortex is associated with hypotension. Conversely, neoplasm of the adrenal cortex is generally accompanied by hypertension; the elevated blood pressure frequently returns to normal after the offending tumor is removed.² Likewise, excessive administration of desoxycorticosterone

acetate may cause hypertension in patients with Addison's disease,^{9,18,20,31,34} in adrenalectomized animals,³² in normal animals^{3,14,17,27,32} and in hypertensive animals.²⁷ The production of experimental hypertension by compression of the renal artery is impossible in adrenalectomized dogs and adrenalectomy is followed by a prompt fall in the blood pressure of dogs previously made hypertensive by clamping the renal artery.^{1,7,13,24}

At autopsy, the adrenal glands of hypertensive patients are said to reveal hyperplastic or adenomatous changes in the cortex,^{21,22,23,26} the incidence of such morphologic changes being greater than could be accounted for by the factor of age alone.^{19,23} Yet the actual rôle which the adrenal cortex plays in the maintenance of the blood pressure in patients with "essential" hypertension remains obscure.

In the present study, the incidence of morphologic changes in the adrenal cortex of patients with "essential" hypertension was reinvestigated. This was prompted particularly in view of a recent report⁸ which maintained that hypertensives demonstrate no greater incidence of histologic alteration in the adrenal cortex than do subjects with normal blood pressure. In addition, the excretion of one of the end-products of adreno-cortical metabolism (the urinary 17-ketosteroids) was determined in a group of normotensive and hypertensive subjects.

Material and Methods. A review was made of microscopic sections of the adrenals of hypertensive and normotensive patients.* These specimens were prepared by members of the Department of Pathology in the course of routine postmortem examinations. In each instance, the entire cortex was studied grossly for adenomatous or hyperplastic changes. In addition, the width of the left ventricular wall was recorded and hypertrophy was regarded as present if the width exceeded 12 mm.³⁵ The total weight of the heart was taken to be increased if it exceeded the normals of each age group in the tables of Rössle and Roulet.²⁸ A search was also made for evidences of arteriolar sclerosis.

A patient was regarded as having had hypertension if two or more of the following criteria were present: (1) persistent systolic blood pressure of 140 mm. Hg or more, (2) persistent diastolic blood pressure of 90 mm. Hg or more, (3) width of the left ventricular wall exceeding 12 mm. (in the absence of rheumatic or luetic heart disease, and of hyperthyroidism), (4) increased total heart weight and (5) arteriolar sclerosis.

The clinical and necropsy records of 135 patients were thus reviewed. According to the criteria outlined above, 65 were classed as hypertensives and 70 as normotensives.

The second part of this study dealt with the excretion of 17-ketosteroids in normal subjects and hypertensive patients. As is generally known, the 17-ketosteroids are formed primarily from the secretions of the adrenal cortex, but they are also derived in the male from the testicular steroids. Since it is difficult to estimate accurately testicular activity in the male, this phase of the investigation was confined to female subjects in whom the entire 17-ketosteroid output may be considered as derived from the adrenal cortex.

The urinary 17-ketosteroids were determined† (with minor modifications) by the method of Friedgood and Berman¹² which is based on the reaction first described by Zimmerman.³⁷ The final calculations were made from a previously prepared curve using dehydroandrosterone‡ as standard material. In

* With the assistance of John J. Larkin, M.D., Department of Pathology, New York Post-Graduate Hospital.

† With the technical assistance of Julius Wiland, B.S., now Lieutenant, Sanitary Corps, Army of the United States.

‡ The dehydroandrosterone was supplied through the courtesy of Dr. Max Gilbert of the Schering Corporation.

our hands, this procedure gave excellent recoveries of known quantities of dehydroandrosterone added to urine.

Each patient was instructed in the manner of collection and refrigeration of the 24-hour urine specimen. Only one such specimen was collected from each patient, since the 17-ketosteroid excretion is reputed to be quite constant from day to day.^{5,6,11}

For reasons already stated, these studies were confined to female patients; a total of 54 analyses were made. Forty were from hypertensive patients ranging in age from 28 to 70 years with an average systolic blood pressure of 200 mm. Hg (range 150 to 274) and an average diastolic blood pressure of 110 mm. Hg (range 80 to 148). Fourteen analyses were made from normotensive subjects with an age range of 20 to 76 years.

Results. Table 1 shows the incidence of hyperplastic or adenomatous changes in the adrenal cortex in 70 normotensive and 65 hypertensive patients as revealed by gross and microscopic neeropsy material. No difference was found in the incidence of such changes in the two groups.

TABLE 1.—THE INCIDENCE OF HYPERPLASTIC OR ADENOMATOUS CHANGES IN THE ADRENAL CORTX AND THE EXCRETION OF URINARY 17-KETOSTEROIDS IN NORMOTENSIVE AND HYPERTENSIVE SUBJECTS

	Group	
	Normotensive	Hypertensive
Adrenal cortex:		
Hyperplastic or adenomatous changes:		
No. of subjects	33	30
%	47	46
Normal:		
No. of subjects	37	35
%	53	54
Urinary 17-ketosteroid excretion:*		
No. of subjects:		
Total	14	40
17-ketosteroid excretion, mg./24 hrs.:		
2.5-12.5	4	37
12.5-22.0	10	3
Average, mg./24 hrs.	14.2 ± 4.0	8.4 ± 4.3

* The significance of these findings was evaluated by the formula

$$t = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{\frac{N_1\sigma_1^2 + N_2\sigma_2^2}{N_1 + N_2 - 2}}} \cdot \sqrt{\frac{N_1N_2}{N_1 + N_2}}$$

for a small series and t was checked against Fisher's tables.¹⁰ In this formula \bar{x}_1 represents the mean for the normals, \bar{x}_2 the mean for the hypertensives, N_1 the number of normal cases, N_2 the number of hypertensive cases, σ_1 the standard deviation of the normals and σ_2 the standard deviation of the hypertensives. t is 4.35 which represents a significant difference.

In 40 female patients with hypertension, the average daily output of 17-ketosteroids was less than in a control group of 14 normotensives. Four of 14 normal subjects excreted less than 12.5 mg. of 17-ketosteroids in 24 hours, whereas only 3 of the 40 hypertensives exceeded this figure. The significance of this finding was corroborated by a statistical analysis (see footnote, Table 1). In 3 hypertensives, the 17-ketosteroid excretion was relatively high (18.2, 18.7 and 22 mg. in 24 hours, respectively). It is interesting to conjecture that in these patients the hypertension may have had its origin in or at least may have been associated with hyperactivity of the adrenal cortex.

So-called "blood adreno-cortical substances (a-c bodies)" were also determined in the hypertensive and normotensive subjects;* but the results are not detailed here since the significance of such determinations is as yet not clearly defined. The method employed was that of Raab,²⁵ which is a modification of the Shaw³⁰-Whitehorn³⁶ procedure. Apparently, the color reaction utilized in this method is not specific for adrenalin; ascorbic acid is one of several important interfering substances. These a-c bodies do not increase quantitatively in the blood when the blood pressure is elevated during the cold-pressor test in humans nor following the injection of renin in cats; there is, however, a close correlation between the rise in blood pressure and the concentration of a-c bodies in the blood of animals after the intravenous administration of adrenalin.³³ In the present study, the 14 normotensives showed an average of 9.65 ± 3.55 micrograms of a-c bodies in 100 cc. of blood, whereas the 40 hypertensives averaged 9.81 ± 3.13 micrograms. The difference between the two groups was statistically insignificant.

Discussion. The present findings confirm the observation of Dempsey⁸ that nodular or adenomatous hyperplasia of the adrenal cortex is not regularly found in association with hypertension and that it occurs with considerable frequency in non-hypertensive cases. It appears safe to conclude, therefore, that hypertension is not necessarily accompanied by any specific alteration in the histology of the adrenal cortex. Likewise, it has been reported that the size of the adrenal gland is not altered by a preëxisting hypertensive state.^{8,16}

Although the findings presented here indicate that the hypertensive tends to excrete less 17-ketosteroids in the urine than the normotensive, this cannot be taken as evidence of adreno-cortical hypoactivity. Browne and his co-workers⁴ and, more recently, Horowitz and Dorfman,¹⁶ have demonstrated the presence in urine of a substance with cortin-like properties which does not give the color reaction for 17-ketosteroids. Therefore, the evidence given here does not preclude the possibility of adreno-cortical hyperactivity in patients with hypertension. In fact, Selye²⁹ has produced hypertension and renal arteriolar sclerosis in rats by the administration of excessive doses of salt and desoxycorticosterone acetate. If, however, it can be demonstrated that the adrenal cortex of hypertensives does not produce an excess of cortin, the present studies on 17-ketosteroid excretion suggest a hypofunctioning adrenal cortex in patients with hypertension, reflecting perhaps a gland exhausted under the constant strain imposed upon it by the persistent elevation in blood pressure.

Conclusions. 1. There is no difference in the incidence of hyperplastic or adenomatous changes in the adrenal cortex of hypertensive and normotensive subjects.

2. The urinary excretion of 17-ketosteroids is significantly lower in hypertensive than in normotensive subjects.

3. Some theoretical considerations are offered to account for these findings.

* With the technical assistance of Samuel Member, B.S.

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FACTORS INFLUENCING FALSE POSITIVE SEROLOGIC REACTIONS FOR SYPHILIS DUE TO SMALLPOX VACCINATION (VACCINIA)*

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RECENT observations and studies have shown that smallpox vaccination (vaccinia) is capable of producing false positive serologic

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reactions for syphilis. Such reactions are of sufficient frequency and intensity to be a serious source of error in the serologic diagnosis of syphilis.

In 1940, Barnard² reported the case of a young man, recently vaccinated, who gave repeated strongly positive Kahn reactions. Mohr and associates⁶ included a similar case in their report of the causes of biologic false positive reactions. Thomas and Garrity,⁷ by statistical analysis of 20,000 recruits, concluded that smallpox vaccination followed by accelerated and non-immune reactions, was the probable cause for the increase in the incidence of false positive reactions for syphilis. One case was studied in detail.

It remained for Lynch *et al.*⁵ to demonstrate conclusively, that smallpox vaccination was a frequent cause of false positive reactions. In a carefully controlled study on 263 persons with a primary vaccinia, they obtained an incidence of 16% positive individuals by one or more of the Kolmer, Kline, Hinton and Mazzini tests. The intensity of these reactions varied from \pm to $++++$. They appeared in 2 weeks and remained positive for 2 months in most instances. A few persisted for 4 months and one for 5 months. Apparently, individuals with accelerated and immune reactions were not included in the group.

An opportunity for a similar study was presented to us³ recently. An importation of a case of smallpox near the Philadelphia area led to mass vaccination approximating one million persons. A group of individuals was chosen in whom a serologic test for syphilis had been performed within a reasonable time previous to the vaccination. There were 202 individuals ranging in age from 3 weeks to 84 years. Over one-half were between 20 and 30 years of age, consisting mostly of medical students and nurses.

Forty-four individuals developed a primary cutaneous (non-immune) reaction at the site of inoculation, 134 developed a local accelerated (vaccinoid) form and 24 were immune.

Out of 202 individuals on whom a single blood examination was performed, 19 were found to be positive by one or more of the Kolmer simplified complement-fixation test, the Kahn and Mazzini flocculation tests. They were examined from 10 to 57 days following vaccination, but 93.6% were done before the 43rd day. Twenty-five persons who gave a negative reaction 14 days after vaccination, were reexamined 14 days later (1 month after vaccination). Four out of this group were now positive. No doubt additional positive individuals would have been detected if the entire group had been examined in a similar manner.

In all, 24 individuals out of 202 gave a false positive reaction for syphilis, giving an incidence of 11.8%. This figure included all individuals regardless of the type of vaccination reaction. Since the positive serologic reactions were about equally divided between the non-immune and accelerated groups and none occurred in the immune, the percentage of positive individuals would be higher, if the latter immune group were excluded.

The serologic reactions were mostly $++$ or less in intensity (Table 1)

and would be classified as negative or doubtful. However, 22.4% were +++ or stronger. The positive individuals were reexamined at regular intervals. At the end of 60 days, only 8 were still positive, while in 80 days, 4 were weakly positive. Two persisted for 100 days, and all became negative in 120 days.

TABLE 1.—NUMBER AND DEGREE OF INTENSITY OF SEROLOGIC REACTIONS ENCOUNTERED IN 202 INDIVIDUALS FOLLOWING SMALLPOX VACCINATION (FIRST STUDY)

Degree of reaction	=	+	++	+++	++++	Total
Kolmer . . .	2	5	1	..	3	11
Kahn . . .	5	6	3	1	3	18
Mazzini . . .	6	9	8	6	..	29
Total . . .	13	20	12	7	6	58

In order to show that the incidence of false positive reactions in this study was not due to chance alone, a survey was made of the number of positive individuals encountered in the same laboratory for 1000 tests of each type performed. When this figure was employed for calculating the significant difference, when compared to the experimental group of 11.8% in 202 individuals, the difference was found to be highly significant. Furthermore, the reactions persisted in the same individuals and gradually disappeared spontaneously. The smallpox vaccination was the only apparent factor operating.

Reports from other sources have added additional evidence to show that smallpox vaccination is an important cause of biologic false positive reactions for syphilis. Arthur and Hale,¹ in studying 95 soldiers, found that 14 (14.8%) gave a temporary false positive reaction. Their study was begun after the men had been recently vaccinated against typhoid fever, tetanus, smallpox and yellow fever. They concluded that the false reactions were the result of the combined inoculations of the routine Army immunizations.

Lubitz⁴ reported an incidence of 13% positive serologic reactions to one or more tests in 100 individuals with a primary smallpox vaccination reaction. The pattern of the subsequent course of the tests was essentially the same as that followed in studies of Lynch and ours. Lubitz also showed that the positive serums did not give the heterophile antibody test, and storage of the serums for 2 to 17 days at 4° C. produced a marked reduction in the intensity of the serologic reactions when they were repeated. Syphilitic serum, on the other hand, dropped only slightly. Such a finding would imply that storage at low temperature might be used, in part, to differentiate the false from the true type of syphilitic reaction.

Analysis of the Second Study. In January, 1943, the entire student body of a medical school was vaccinated against smallpox. Subsequently, a new freshman class was enrolled, leaving three-fourths with a recent vaccination. Six months later the students were again subjected to vaccination, not only to smallpox, but to typhoid, paratyphoid fevers and tetanus. Since smallpox vaccination was given after the administration of typhoid vaccine and 2 injections of tetanus toxoid, an opportunity was offered to determine just what rôle such

immunization played in the production of false positive reactions for syphilis. It also offered additional data for the continued study of smallpox as a cause of false positive reactions. Other factors were also studied.

The second group for study was composed of men between the ages of 21 and 30 years. It included 323 individuals, three-fourths of whom were vaccinated for smallpox 6 months previously. Following a preliminary blood test they were revaccinated. Six individuals developed a primary cutaneous (non-immune) reaction, 71 developed an accelerated (vaccinoid) form, and 246 were immune. One month after the date of vaccination, a blood specimen was obtained and examined with the Kolmer, Kahn and Mazzini tests. No opportunity was offered for more frequent and prolonged observations. There were 15 individuals with 21 positive serologic reactions. Five of these occurred in the accelerated and 4 in the primary (non-immune) group, while 6 were immune. The serologic reactions in this study were mostly ++ or less in intensity. Twenty per cent were +++ or stronger, and occurred in the accelerated and primary (non-immune) types.

The large number of immune individuals in this second study contained 2.4% of weakly positive serologic reactions. The combined total for the accelerated and primary individuals amounted to 11.7%, which is almost identical with that of the first study (11.8%). The serologic tests taken before vaccination and used as control revealed an incidence of 1.6% positive individuals. These tests were done after typhoid and tetanus immunizations. Thirty days after vaccination, and including all individuals regardless of their vaccinia cutaneous reactions, 4.6% were positive. On this basis alone there is a significant difference in the increase which can be attributed to smallpox vaccination.

Summarizing the pooled data (Table 2) on 525 individuals, using a single blood test 30 days after vaccination, there were 270 immune cutaneous vaccinia reactions with 6 weakly positive individuals (2.2%). Out of 205 accelerated reactions 15 (7.3%) were positive, while 13 (26%) out of 50 primary (non-immune) were positive and included most of the strongly false positive tests for syphilis. Excluding the immune, 11% of the individuals with an accelerated or non-immune cutaneous vaccinia reaction were positive by one or more of the Kolmer, Kahn and Mazzini tests.

TABLE 2.—CUTANEOUS VACCINIA REACTIONS AND SEROLOGIC RESPONSE IN EACH TYPE, WITH A SINGLE SPECIMEN OF BLOOD AFTER 30 DAYS (COMBINED STUDY)

	Type of vaccinia reaction			
	Immune	Accelerated	Non-immune	Total
Number of individuals	270	205	50	525
Individuals with positive tests	6	15	13	34
Per cent	2.2	7.3	26	6.5

Per cent positive of accelerated and non-immune individuals, 11.

In view of Arthur and Hale's work¹ in which the false positive reactions were attributed to the combined effects of typhoid, tetanus,

smallpox and yellow fever immunizations, an attempt was made to clarify this problem. Smallpox vaccination alone is capable of producing false positive reactions for syphilis in 11 to 16% of individuals. No clear-cut evidence is available to show that other forms of immunization are capable of doing the same thing.

To verify experimentally if multiple immunizations, excluding smallpox, can produce similar false positive serologic reactions, the following investigation was undertaken. There were 314 men who had received a Kahn serologic test just prior to the first injection of typhoid (T.A.B.) vaccine and tetanus toxoid. Twelve days after the last of the 3 weekly inoculations of typhoid (T.A.B.) and 10 days after the second and 31 days after the first inoculation of tetanus toxoid, a sample of blood was obtained for serologic examination. Five individuals, giving an incidence of 1.6% had weakly positive serologic reactions. No test gave a stronger reaction than + in this group. In view of these findings, it cannot be said that typhoid and tetanus immunizations contribute materially to the problem of false positive reactions for syphilis.

The question arises whether non-specific stimulation with other antigens might cause a rise in the pseudo-syphilitic reagin of an individual who had been recently vaccinated and had developed a false positive serologic reaction. It was possible to assemble a group of 5 individuals who gave a false positive syphilitic reaction 6 months previously. They gave 8 positive reactions by one or more of the Kolmer, Kahn and Mazzini tests. In no instance were these individuals positive after immunization with typhoid vaccine and tetanus toxoid. A control group consisting of 17 men with similar vaccinia reactions and negative blood 6 months previously also failed to show any positive syphilitic reactions.

Since the majority of individuals had been vaccinated 6 months previously, what effect would revaccination have on the serology of those who gave false positive tests originally? Six individuals were available whose data were comparable (Table 3). All of the persons had returned to normal serologic tests 3 months previously and had a negative serologic reaction for all tests, before revaccination. Fourteen days following revaccination 1 gave a ++ Kolmer while another gave a ++ Mazzini. These returned to normal in 30 days, although 1 of the 2 showed a = Mazzini at this time. The number of cases studied is not sufficient to draw conclusions, but can be used as a nucleus for further investigation.

TABLE 3.—SEROLOGIC RESPONSE FOLLOWING REVACCINATION OF PREVIOUSLY POSITIVE INDIVIDUALS

Case No.	Serologic tests 14 days after original vaccination			Serologic tests 6 months later			Serologic tests 14 days after revaccination			Type of cutaneous vaccinia reaction
	Kol.	Kahn	Maz.	Kol.	Kahn	Maz.	Kol.	Kahn	Maz.	
15	+	++	++	—	—	—	—	—	—	Immune
23	+	—	—	—	—	—	—	—	—	"
25	=	—	—	—	—	—	—	—	—	"
52	—	—	++	—	—	—	—	—	++	"
55	++	—	+	—	—	—	++	—	—	"
102	++++	++++	+++	—	—	—	—	—	—	"

It has been pointed out that the sera of individuals with false positive tests for syphilis have a rapid loss of the reagin which produces such

reactions. Lubitz, using the Kahn test, found that after standing in the ice-box at 4° C. for 2 to 17 days the titer of the serum fell appreciably, a + + + + reaction falling to + +, + or negative. The weaker positives fell proportionately. The titer of the serum from syphilitic patients remained the same or dropped slightly.

Five of our sera were retested after storage for 7 months in the ice-box at 4° C. Table 4 shows the result. The Kahn test showed an appreciable decrease in the weaker positives, but the Kolmer and Mazzini tests retained their sensitivity with only some decrease in the weakly positives. Our sera were not inactivated before storage.

TABLE 4.—SEROLOGIC TESTS ON POSITIVE UNALTERED SERUM AFTER STORAGE AT 4° C. FOR 7 MONTHS

Case No.	Original tests (2-5-43)			Tests 7 months later (9-7-43)		
	Kol.	Kahn	Maz.	Kol.	Kahn	Maz.
9 . . .	+	—	++	++	—	±
15 . . .	—	+++	+++	±	+	++
32 . . .	—	++	++	—	±	±
55 . . .	++	—	+	+	—	+
102 . . .	++++	++++	+++	++++	+++	++++

Comment. The total of both groups so far studied is 525 individuals, the majority of whom were male adults between 20 and 30 years of age. To draw accurate conclusions as to the incidence of biologic false positive tests for syphilis due to smallpox vaccination, several factors must be taken into consideration, one being the type of vaccination reaction. Lynch *et al.* basing their study on primary reactions, found 16% positive individuals with the use of multiple serologic tests, while Lubitz, who apparently employed only one serologic test, found 13% positives in primary reactions and none in accelerated and immune. In the 26 cases of Thomas and Garrity, who also employed the Kahn test only, 3 were immune, while the other 23 were about equally divided between the non-immune and accelerated. Twenty-four immune individuals in our first study were all negative.

In our second study, however, 6 out of 246 immune individuals (2.4%) gave weakly false positive serologic reactions. There are several possibilities for this finding. First of all, smallpox vaccination with an immune cutaneous response may be capable of producing such reactions. Secondly, this low incidence may be representative of the general population of the same age group by the techniques employed. Thirdly, recent revaccination may produce a detectable increase in the reagin of a previously positive individual. Such suggestive evidence has been presented in this study in a very small number of individuals, too small to draw conclusions.

From a practical clinical standpoint, it is extremely important to correlate the incidence of false positive tests of the blood with each type of vaccinia cutaneous reactions. A person with a positive syphilitic blood test who has been vaccinated recently, is quite likely to remember, on questioning, as to whether or not a scab was formed. If there is no history of a scab, the reaction may be considered as immune

and the serologic test interpreted accordingly. If, however, a scar was formed, denoting an accelerated or non-immune (primary) reaction, vaccination should be suspected as a probable cause of the positive syphilitic serologic test. The presence or absence of a vaccination scar cannot be relied upon entirely as evidence of the type of skin reaction, since many accelerated reactions may leave little or no marking within the period of the presence of a false positive test for syphilis.

The decrease in the intensity of the serologic reactions on storage at 4° C. as observed by Lubitz in the interpretation of the tests may be of some value. Since such a decrease occurs appreciably with one serologic test and only slightly with others, the value of this observation is minimized.

The transitory nature of false positive reactions is the most important characteristic in the differential interpretation so far. The vast majority disappears in 60 days. Very few persist for a longer period, and then only as a weak reaction of + or less. This has been the experience of other investigators already cited.

In view of Arthur and Hale's report, it was desirable to analyze the probable causes of such false reactions which follow routine Army immunizations. Typhoid (T.A.B.) and tetanus immunizations were not found to contribute materially to the incidence of false positive reactions for syphilis. Thomas and Garrity found that typhoid inoculations had no bearing on the false positive Kahn diagnostic test. Observations on a limited number of cases also demonstrated that immunization with these antigens did not reactivate a false positive test in individuals who gave such tests from accelerated and non-immune vaccinia vaccinations 6 months previously.

The ability of smallpox revaccination within 6 months to reactivate a false positive reaction for syphilis requires additional investigation. Two individuals, out of 6 studied, again gave false positive tests which disappeared in 30 days. The cutaneous vaccinia reactions in all 6 were of the immune type. The blood serology prior to revaccination had returned to normal. Obviously, this phase of the problem is extremely important, and requires much additional data to prove conclusively if findings in such a small series are due to chance or to actualities.

Summary. 1. Smallpox (vaccinia) vaccination followed by an accelerated or primary (non-immune) cutaneous response is a newly recognized and important cause of biologic false positive serologic reactions for syphilis. The incidence of such reactions is at least 11 to 16%.

2. The available evidence justifies the conclusion that an immune response to smallpox vaccination can be disregarded as a significant cause of a false positive serologic reaction for syphilis.

3. The false positive serologic reactions for syphilis are transitory. They appear within 2 weeks of the date of vaccination and disappear, in most instances, within 2 months. A few persist as extremely weak reactions as long as 4 months.

4. Typhoid (T.A.B.) and tetanus toxoid immunizations have no

significant bearing on the production of false positive serologic reactions for syphilis.

5. Suggestive findings are presented to show: (a) that recently vaccinated individuals who gave a positive serologic reaction, do not have a reactivation of their positive reactions following typhoid and tetanus immunizations 5 months later, and (b) individuals with a false positive serologic reaction, when revaccinated for smallpox within 7 months, may again present a weak serologic false positive response for syphilis, even though the second vaccinia reaction is of the immune type.

6. Positive serums stored in the ice-box at 4° C. for 7 months have a variable loss of titer. Such loss is not sufficient to be of differential diagnostic value.

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PHOSPHORUS POISONING

A REPORT OF 16 CASES WITH REPEATED LIVER BIOPSIES IN A RECOVERED CASE

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POISONING due to phosphorus is regarded as uncommon in the United States. Reports of only 9 fatalities could be found in our medical journals in the past 2 decades,^{4,5,6,9,10,15,20,27,30,31} but in 1927 the American Museum of Safety listed the deaths of 16 children who ate fireworks.^{7,24} These reports, together with the 4 fatalities reported here, suggest that the incidence of phosphorus poisoning may be greater than that indicated by a careful perusal of our medical literature.

The relative infrequency of phosphorus poisoning in the United States is probably due to the prohibition of the manufacture and sale of matches made from yellow phosphorus. In China¹³ and Japan,²² where the sale of this type of match is permitted, the number of cases of phosphorus poisoning has increased in recent years. One milligram of yellow phosphorus per kilo of body weight is usually fatal, while red phosphorus is relatively nontoxic even in large amounts.⁸

Yellow phosphorus-containing roach poisons and fireworks are still available in the United States and represent an obvious danger to children. Five of the 9 fatalities reported in the American literature resulted from the ingestion of small amounts of fireworks by children.^{5,6,10,20,27} The other 4 fatalities were due to the taking of roach poison.^{4,9,15,30,31} Roach poison containing about 2% yellow phosphorus is widely sold at most drug and grocery stores.

At Charity Hospital in New Orleans, 16 patients, 4 of whom died, have been treated for phosphorus poisoning since 1920. This represents an incidence of 1 in every 57,700 admissions. The purpose of this paper is to report the clinical picture of phosphorus poisoning in these patients and to discuss in detail the case of 1 surviving patient in whom morphologic liver damage is apparently progressing to portal cirrhosis.

Case Reports. Fatalities. CASE 1. C.C., a 9 month old negro male child, ate a piece of potato covered with a layer of roach poison and died 10 hours later. There were no gastro-intestinal symptoms, but the child was semicomatose when seen at the hospital 4 hours after having ingested the poison. His temperature was 101.2° F. and his pulse rate 145 per minute, with respirations 45 per minute. Gastric lavage was done at once and 100 cc. of 5% glucose with 100 cc. of normal saline were given, but the infant died 6 hours after admission. The diagnosis made by the coroner at autopsy was phosphorus poisoning.

CASE 2. M.G., a 65 year old housewife, swallowed one teaspoonful of roach poison and died 52 hours later. She was admitted to the hospital 12 hours after having taken the phosphorus-containing poison and gastric lavage was immediately performed. Throughout the day she complained of epigastric pain and progressive weakness. She was semistuporous, weak and in shock, with a blood pressure of 60/40 mm. Hg and a pulse rate of 120 per minute. The low blood pressure continued despite a blood transfusion of 500 cc. and the intravenous administration of 100 cc. of gum acacia in 400 cc. of saline. The patient received 1200 cc. of fluid and excreted 600 cc. of urine. On the day of death the blood urea nitrogen was 46 mg. per 100 cc.; creatine was 5.3 mg. per 100 cc. and the blood sugar was 139 mg. per 100 cc. There was a trace of albumin in the urine and 2 to 3 red blood cells and 4 to 6 white blood cells were seen per high-power field. The coroner's diagnosis was phosphorus poisoning.

CASE 3. Y.R., a 20 year old white housewife, was brought to the hospital in a state of coma and died on the same day that she had taken an undetermined amount of roach poison. The coroner's diagnosis was phosphorus poisoning.

CASE 4. J.R., a 15 month old infant, was admitted with a history of 5 days' abdominal pain and intermittent vomiting which had not been severe enough to keep her from play. On the evening of the 4th day she became comatose. She was in deep coma when admitted to the hospital on the 5th day and vomited coffee ground material shortly afterwards. She was jaundiced and stuporous and on one occasion drew her head and neck back so that she appeared opisthotonic. No true convulsions were seen. The family was unable to say whether the child had taken poison of any kind but admitted that roach paste had been "set out." A spinal tap was done and clear fluid under normal pressure was obtained. The child died just as the needle was withdrawn.

Spinal fluid examination and urinalysis were normal. The blood sugar was 99 mg. per 100 cc., the blood glucose 27 mg. per 100 cc. and the carbon dioxide combining power 30 volumes per cent. The icterus index was 50.

At necropsy the heart weighed 40 gm. and appeared to be slightly dilated. The myocardium was pale. Slight atelectasis of the posterior portion of both lungs was noted. The liver weighed 500 gm. (normal weight at 15 months, 330 gm.), was 5 cm. below the costal margin, bright yellow in color, and a loss

of lobular arrangement was seen on cut section. No gross abnormalities of the pancreas, kidneys, adrenals or spleen were noted. The brain weighed 700 gm.; its gyri were flattened and its sulci narrowed.

Significant microscopic abnormalities were seen in the liver, kidney and brain. In the liver, there was extensive fatty metamorphosis with vacuolization of almost all the liver cells about the portal areas. The rest of the liver cells were swollen and granular. Moderate polymorphonuclear leukocytic and lymphocytic infiltration was seen in some of the portal spaces, but there was no connective tissue proliferation. In the kidney the cells of the tubules were granular and swollen, narrowing the lumen of the tubules markedly and closing it entirely in some portions. Each renal epithelial cell showed numerous very small vacuoles. The glomeruli were normal. The brain showed moderate congestion of the vessels in the leptomeninges and in the brain substance. There was no evidence of inflammatory cell infiltration in either of these locations. An occasional vessel showed a collar of recent hemorrhage in the perivascular space. Vacuolization of the brain matrix and "lacunization" of the nerve cells indicated cerebral edema.

Recoveries. CASE 5. M.B., a 30 year old housewife, took 1 ounce of roach paste containing phosphorus with suicidal intent. Twenty minutes later she developed epigastric fullness, became nauseated and vomited. She vomited frequently for 4 or 5 hours and then developed a profuse watery diarrhea which was accompanied by abdominal cramps that kept her awake all night. She continued to vomit everything taken by mouth, but the diarrhea subsided after 6 hours. She was admitted to the hospital 18 hours after having taken the poison. Her stomach was pumped out immediately and she was given 1000 cc. of 10% glucose intravenously. She was emaciated, complained of abdominal pain and the upper abdomen was moderately tender to deep palpation. The blood pressure was 100/80 mm. Hg, the pulse 105 per minute and the temperature 101° F. The blood and spinal Wassermann tests were strongly positive and a 1-plus sugar and a trace of albumin were found in the urine. Symptoms cleared rapidly and except for a slight temperature for 3 days the patient had no complaints. No jaundice was seen.

CASE 6. E.M., a 30 year old white female, took an undetermined amount of roach paste containing phosphorus on a slice of bread. Almost at once she developed violent cramping abdominal pains. Gastric lavage was done 3 hours after the poison had been taken and 4 ounces of mineral oil with 2 ounces of 50% magnesium sulfate were left in the stomach. The blood pressure was 100/70 mm. Hg, the abdomen moderately tender to deep palpation and the liver could just be felt. No jaundice was noted. Routine urinalysis and blood studies showed no abnormalities. The patient was given 3 infusions of 1000 cc. of 5% glucose in the first 24 hours. During this time she complained of abdominal cramps and passed 8 watery stools. She had a few cramping pains during the next 3 days, but was otherwise well at the time of discharge on the 5th day.

CASE 7. E.W., a 35 year old male, took rat poison containing 2.5% phosphorus with suicidal intent. He was admitted to the hospital 12 hours later in a state of coma. Gastric lavage was done immediately and a solution of 2.5% magnesium sulfate was left in the stomach. An intravenous infusion of 3000 cc. of 10% glucose was administered. The patient was restless and vomited frequently. A few superficial ulcers were noted on the reddened mucous membrane of his mouth and tongue. There was slight epigastric tenderness. On the 2nd day the symptoms had disappeared and he was discharged on the 5th day. Jaundice was not seen.

CASE 8. G.M., a 23 year old housewife, took 2 teaspoonsful of roach paste in an attempt at suicide. Her physician was called at once and he administered 11 glasses of salt water which caused the patient to vomit profusely. Then a dilute mixture of copper sulfate, potassium permanganate and turpentine was left in the stomach. Six hours later the patient was admitted to the hospital in no acute distress but with a blood pressure of 98/54 mm. Hg.

She vomited 11 times on the 1st day, 8 times on the 2nd and complained of

mild abdominal cramps and generalized body aches. She was given 1000 cc. of 5% glucose on the 3rd day and had no complaints. Jaundice was not seen and she was discharged on the 7th day.

The admission laboratory findings were 3-plus albuminuria, occasional granular casts in the urine with blood levels of 52.5 mg. of non-protein nitrogen per 100 cc., 25 mg. of urea per 100 cc. and 105 mg. of sugar per 100 cc. On the 3rd and 7th days the urine was negative and the blood urea had fallen to 15 mg. per 100 cc. of blood on the 7th hospital day.

CASE 9. F.C., a 39 year old white housewife, took an undetermined quantity of roach poison with suicidal intent. She was admitted to the hospital on the same day and was semistuporous and restless. Immediate gastric lavage was done and the patient vomited clear, phosphorescent fluid 3 times. She was completely well on the following day and left the hospital.

CASES 10 to 15. Six other patients who took undetermined amounts of roach poison recovered quickly. The patients were 2 white males, aged 25 and 42; 1 white female aged 51; 2 infant girls aged 18 months and 1 year; and a 3½ year old boy. All had a gastric lavage within 2 hours after taking the poison and exhibited no symptoms except mild nausea. All were discharged from the hospital within 10 to 20 hours after admission.

CASE 16. G.A., a 61 year old unemployed white male, swallowed an ounce of roach paste containing 2% phosphorus at 12:30 A.M. on April 2, 1942. Within 30 minutes he began to vomit, but between paroxysms he managed to consume another ounce of roach paste. The vomiting became increasingly severe and he developed cramping abdominal pains and began to pass frequent stools which were first solid and then watery and later contained dark red masses "like Concord grapes." The vomitus and stools were put in the same container and emitted a greenish blue light. Vomiting subsided but the diarrhea and abdominal pain persisted throughout the first 48 hours. On the morning of April 4 the patient's landlady found him in a semistuporous state with several self-inflicted lacerations on his left wrist.

He was admitted to the hospital at 4:25 P.M. on April 4, 64 hours after having taken the poison, semicomatose and deeply jaundiced. The blood pressure was 92/62 mm. Hg, the pulse 120 per minute and the temperature 96° F. The liver was felt 6 cm. below the costal margin in the mid-clavicular line. Superficial cuts were noted on the left wrist and many shallow ulcers were seen on the mucous membrane of the mouth, tongue and oral pharynx.

Gastric lavage was done immediately and 100 cc. of mineral oil were left in the stomach. The patient was then given 2000 cc. of 10% glucose intravenously and this was repeated at least once daily for the first 10 days. An eggnog mixture containing 60 gm. of protein, 300 gm. of carbohydrate and 30 gm. of fat was administered each day by duodenal intubation. Vitamin concentrates and 2 oz. of mineral oil were also given. After 10 days the patient was able to eat and was placed on a diet containing 450 gm. of carbohydrate, 120 gm. of protein and 70 gm. of fat.

Throughout the 1st week the patient was semistuporous. He vomited occasionally and passed 15 to 20 loose involuntary stools daily during the 1st week and 4 to 5 stools daily for the next 5 days. These were clay colored from the 5th to the 9th hospital days. Three blood transfusions were given during the 1st week. He was markedly jaundiced during this period and the liver was felt 6 to 8 cm. below the costal margin. After the 19th day of illness, improvement was quite rapid and 30 days after the ingestion of the poison the jaundice had markedly diminished and the liver was just palpable. Early in the 7th week there was a 1-plus pitting edema of the ankles, but this disappeared with continued rest in bed. The patient was discharged well on May 28, 1942, the 54th hospital day. He was readmitted for study on July 1, 1942, feeling "perfectly well." At this time all laboratory tests gave results within normal limits. The liver was barely palpable and the spleen could not be felt.

Pertinent laboratory findings are given in Tables 1 and 2. The hemoglobin varied between 10 and 12 gm. per 100 cc., the red blood cell count between 3.2 and 5.4 millions per c.mm. Studies of the morphology of the blood and

bone marrow cells showed only a mild toxic reaction. During the 2nd week of hospitalization the white blood count varied between 11,000 and 16,000, but later it was within normal limits. The levels of the blood calcium and phosphorus were not abnormal and the prothrombin time was normal on April 11 and 21. On May 1, the intravenous bromsulfthalein test showed 50% retention in 5 minutes and 30% in 1 hour. On May 13 there was no retention at the end of 30 minutes. The hippuric acid test was normal on May 17 and July 1.

TABLE 1.—CASE 16, SHOWING THE FINDINGS IN THE URINE AND STOOLS AND INDICATING THAT THERE WAS COMPLETE BILIARY OBSTRUCTION FROM APRIL 10 TO 15, 1942

Urinalyses				Stool analyses		
Date (1942)	Bilirubin	Urobilinogen	Microscopic	Date (1942)	Color	Stercobilinogen
4-5 (3rd day)	Tr.	+1:10	Few crystals, no WBC or RBC	4-6	Black	1+
4-8	4+	-1:10	Many WBC, few hyaline and gran. casts	4-8	Brown, watery	1+
4-10	4+	None	Bile-stained casts	4-9	White	Tr.
4-12	4+	None	Tyrosine crystals 4+, gran. and hyaline casts	4-10	Soft, chalky white	0
4-14	4+	None	Same	4-12	Same	0
4-15	4+	Faintly positive	10 WBC per hpf, occ. gran. cast (bile stain+)	4-13	Same	Tr.
4-16	3+	+1:10	20 WBC, occ. gran. cast (coarse)	4-14	Pale yellow	1+
4-17	3+	+1:40	5 WBC per hpf	4-17	Liquid yellow	1+
4-19	+	+1:640	Occ. WBC	4-18	Golden yellow	4+(1:160)
4-21	+	+1:320	10 WBC per hpf	4-23	Yellow	+1:320
4-22	+	+1:160	Few epith. cells, no WBC per hpf	4-29	...	+1:80
4-23	=	+1:80	12 WBC per hpf			
4-25	0	+1:10	-			
4-29	0	+1:10	-			
7-6	0	+1:10	Neg.	7-6	Yellow	Strongly +
9-14	0	+conc.	Neg.			

The patient was readmitted September 24, 1942, complaining that pus had been draining from his right ear for 2 days. The sclerae were slightly yellow and the right ear drum was injected and perforated. The liver was barely palpable on deep inspiration, but the spleen could be felt for the first time. The icteric index was 15.6 and the blood bilirubin too low to read. The intravenous hippuric acid test showed slight impairment of liver function (Table 2). He was discharged apparently well on the 5th hospital day and was advised to continue to take the high-protein, high-carbohydrate diet previously prescribed.

Liver Biopsy Studies of Patient No. 16. *First Biopsy* (33rd day of illness). The specimen consisted of a cylindrical piece of liver tissue which measured about 1 cm. in length and 0.1 cm. in diameter. No gross changes were noted. Microscopic serial sections were made. The general architecture was preserved. The cytoplasm of the liver cells had a foamy appearance and showed a moderate degree of vacuolization. An occasional area of focal necrosis (Fig. 1) was noted which consisted of several necrotic liver cells infiltrated by a few polymorphonuclear leukocytes. The largest of these areas measured about 60 microns through the greatest diameter. Finely granular, yellowish brown pigment was present within the cytoplasm of the Kupffer cells and of the liver cells. The pigment was rather uniformly distributed throughout the liver lobules. The periportal connective tissue was somewhat increased in quantity (Fig. 2) and was infiltrated with a moderate number of polymorphonuclear leukocytes. The bile ducts were not necrotic and contained no inspissated bile. Special stains revealed that some of the pigment within the liver cells contained iron, and hence was hemosiderin. The majority of the pigment granules, however, was neither hemosiderin nor hemofuscin.

TABLE 2.—CASE 16, SHOWING THE BLOOD CHEMICAL FINDINGS, WITH FIRST AN INCREASE AND THEN A DECREASE IN THE ICTERUS INDEX; THE LIVER FUNCTION TEST; AND BLOOD AND MISCELLANEOUS STUDIES

Date (1942)	Blood chemistry*						Liver function tests				Blood count*				
	Urea	Glu- cose	CO ₂	Chlo- rides	P	Bilirubin	Icterus index	Total serum proteins	Bromsulph- thalein	Cephalin floccula- tion	Hippuric acid*	Prothrom- bin time	Hgb.	RBC (in millions)	WBC
4-6	51.6	133	17.5	125.0	12.0	4.0	6,728
4-10	3.3	..	125.0	+++
4-11	20.0	..	37	..	3.6	21.8	166.0	4.5	14,000
4-13	20.0	562	3.3	4.07
4-16	54	562	..	8.8	143.0	4.77	13.2	3.41	18,050
4-20	15.7	87	Normal
4-21
4-23	7.4	50.0
4-29	35.0	..	30%—1 hr.	+	12.0	3.94	8,320
5-4	0%—1 hr.
5-13	Neg.
5-18	22.8	5.11	0.54 mg.
5-19	0.82 mg.	..	11.5	3.6	5,250
6-26	15.1	114	48	cholesterol 166	..	6.51	...	Neg.
7-6	too low to read	..	9.2
9-24	"	..	15.6	6.51	0.73 mg.	..	13.0	4.6	4,700

Miscellaneous Blood Studies (Bone Marrow and Blood Morphology. 4-17-42: WBC show marked shift to left with toxic granules. Bone marrow appear slightly hyperplastic and shows a granulocytic, myelocytic stimulation. Bleeding and clotting times normal on 4-5-42. K & K negative (unsatisfactory). Sed. rate 18 mm. per hr. on 4-13-42. 4-21-42: Kline and Kolmer strongly +. Spinal fluid K & K negative. 4-29-42: K & K strongly +.

* Intravenous hippuric acid test.

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Second Biopsy (45th day of illness). The specimen consisted of a cylindrical piece of liver tissue which measured about 1 cm. in length and about 0.1 cm. in diameter. No gross changes were noted. Microscopic serial sections were made. The general architecture was preserved. No areas of focal necrosis were present but some of the liver cells showed vacuolization of their cytoplasm. The quantity of periportal tissue was increased over that which was seen in the first biopsy. It showed finger-like extensions of fibrosis entering the liver parenchyma for distances equaling the diameter of 6 to 8 liver cells (Fig. 3). A moderate number of polymorphonuclear leukocytes as well as lymphocytes infiltrated the connective tissue. The type distribution of pigment was similar to that seen in the first biopsy.

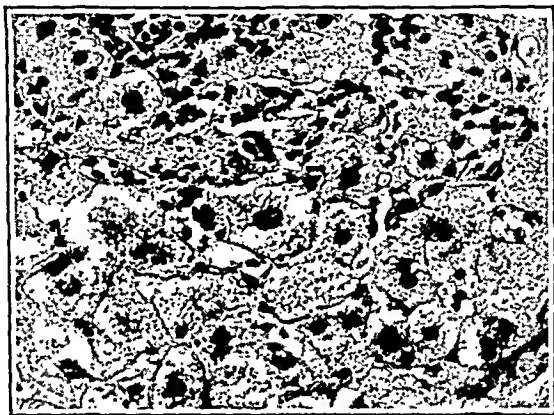


FIG. 1.—Photomicrograph of center of liver lobule showing small area of focal necrosis. Biopsy 33 days after onset of illness. H. and E stain. ($\times 276$.)



FIG. 2.—Photomicrograph of portal canal showing inflammatory cell infiltration into the supporting connective tissue. Biopsy 33 days after onset of illness. H. and E stain. ($\times 276$.)

Third Biopsy (86th day of illness). The specimen consisted of a cylindrical piece of tissue which measured about 0.3 cm. in length and 0.1 cm. in diameter. No gross changes were noted. Microscopic serial sections were made. The general architecture was somewhat distorted because of the periportal fibrosis.

Only a few vacuoles were noted in the cytoplasm of the liver cells and no foci of necrosis were present. The quantity of the periportal connective tissue was greater than that noted in the previous biopsy. The connective tissue extended further out into the liver parenchyma and in some places the connective tissue of two portal spaces joined each other (Fig. 4). A moderate number of inflammatory cells, the majority of which were lymphocytes, were present in the periportal connective tissue. A few polymorphonuclear leukocytes were also present. There was no change in the type and distribution of the pigment.

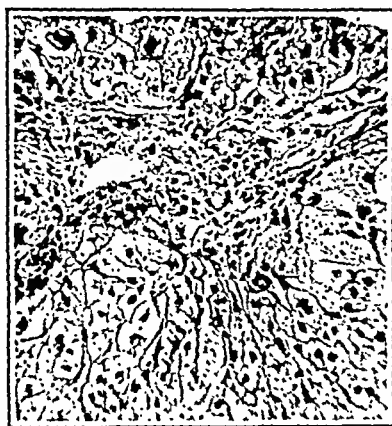


FIG. 3.—Photomicrograph of portal canal showing finger-like extensions of fibrosis entering the liver parenchyma. Biopsy 45 days after onset of illness. H. and E. stain. ($\times 144$.)

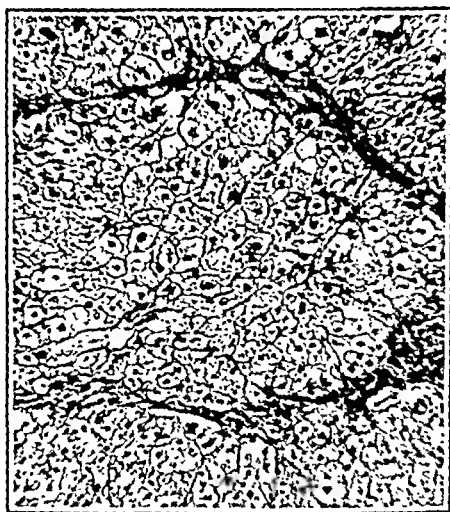


FIG. 4.—Photomicrograph showing the fusion of fibrotic extensions of adjacent portal canals. Biopsy 86 days after onset of illness. H. and E. stain. ($\times 86$.)

Fourth Biopsy (191st day of illness). The tissue measured about 1.5 mm. in length and 0.5 mm. in width. Microscopic serial sections were made. Two portal canals were present in this fragment of tissue. The liver cells were fairly well preserved and showed only a few very small vacuoles in their cytoplasm. The quantity of periportal connective tissue was similar to that which was observed in the last biopsy but the collagen content was greater.

Comment. The diagnosis of phosphorus poisoning rests upon a history of the ingestion of phosphorus, the recovery of phosphorus from the vomitus or stools and the presence of toxic symptoms. In most instances, the history of ingestion of phosphorus, the characteristic odor and phosphorescence of the vomitus or stools, the occurrence of severe abdominal pain, emesis, icterus, ecchymosis, coma or convulsions, permit easy diagnosis. In the absence of a history, accurate diagnosis is difficult.

According to Thayer and Wolf,²⁹ symptoms appear soon after the ingestion of the poison in only 10 to 15% of the cases. Hours and even days may elapse in the majority of instances before symptoms of poisoning occur. Abdominal pain, nausea, emesis, thirst, jaundice, diarrhea, ecchymosis, coma, delirium and convulsions are, in the order named, the most frequently encountered symptoms. Abdominal tenderness, enlargement of the liver and stupor or coma are the usual physical findings. Laboratory studies may reveal uremia, anemia and evidence of liver damage.

In our patients, symptoms were noted soon after the ingestion of the poison in 4 cases and late in 4 cases. The remaining patients had seen a physician soon after taking the poison. Abdominal pain, nausea, emesis, weakness, diarrhea and coma were the most frequently noted symptoms. Jaundice was seen only twice. Generalized abdominal tenderness was noted in 8 cases and enlargement of the liver in 2.

Six of our patients admitted having taken the poison with suicidal intent; 4 took it accidentally. In Europe, many suicides due to the ingestion of phosphorus have been reported,^{3,11,19,23,28} but only 1 of the 9 fatalities reported in our literature was listed as suicide.

Ten to 15% of patients taking yellow phosphorus die within 24 hours and 85% within 7 days.²⁹ Early death is apparently due to shock resulting from the general toxic effect of the poison on body cells. The same clinical picture preceding death is often observed in patients who take mercury.¹⁷ Patients 1 and 2 were admitted to the hospital in a state of shock and coma and died 10 and 12 hours respectively after taking roach paste. Patient 3, who survived 52 hours after taking roach paste presented an identical picture. None of these 3 patients showed characteristic postmortem changes.

Fatal cases that survive more than 3 to 4 days usually show definite evidence of liver damage (jaundice, urobilinogenuria, bilirubinuria and coma). Fatty metamorphosis of the liver and tubular damage in the kidneys are the usual morphologic findings. Patient 4 was jaundiced and comatose and at necropsy showed fatty metamorphosis of the liver, tubular damage to the kidneys, and evidence of cerebral edema.

Patient 16 had complete obstruction of the outflow of bile from the liver for 4 days, evidenced by the total absence of bile pigments in the stool and of urobilinogen in the urine (Table 1). With the reappearance of bile pigments in the stools and urobilinogen in the urine, the liver became smaller. This temporary complete obstruction to the outflow of bile was probably due to swelling of the liver parenchyma as well as the periportal inflammatory reaction. The persistence of the jaundice

was probably due to impairment of liver cell function. This patient has been followed in the clinic for 9 months and feels perfectly well. Moreover all the tests of liver function are within normal limits. His liver, once palpable 8 cm. below the costal margin, can no longer be felt and spider angiomas have not been seen. However, after 9 months his spleen has become palpable.

Twelve of our patients recovered, 6 without any symptoms except mild nausea and discomfort. Six complained of nausea, moderately severe emesis and abdominal cramps. All vomited spontaneously 20 to 60 minutes after taking the poison and later had a gastric lavage. It is not difficult to know definitely why these 12 patients survived and the other 4 died, since all 12 of these patients vomited promptly after taking the poison or had the poison washed from the stomach within 2 hours. This appears to us to be the deciding reason for their survival. The 4 patients who died failed to vomit until 10 hours after the poison had been taken. Our histories are not accurate enough to detect any differences in the amount of poison taken.

Treatment demands immediate removal of the poison from the stomach, as well as measures to prevent absorption of phosphorus. Oxidation of the phosphorus with potassium permanganate, hydrogen peroxide, oil of turpentine and copper sulfate have been tried but not established as effective.²⁶ Atkinson² has shown that the administration of mineral oil to dogs a few minutes before or after feeding phosphorus will save the animals. Phosphorus is soluble in the mineral oil which is not absorbed from the gut, so it would seem advisable to leave 100 to 200 cc. of mineral oil in the stomach after lavage. Potassium permanganate (1:5000 sol.) can be left in the stomach to convert yellow phosphorus to harmless phosphates.

Once absorption has taken place, the treatment must be directed as far as possible to sparing the organs most severely damaged by phosphorus, that is, the liver and kidneys. It has been demonstrated that a high-protein, high-carbohydrate and low-fat diet will protect animals from toxic liver injury.^{12,16,18,21,25,32} A diet such as that given Case 13 (450 c., 120 P., 70 F.) should be administered each day, supplemented by a high intake of vitamin B complex, with a fluid intake of at least 3000 cc.

Patient 16 is of special interest because we were able to follow by means of repeated liver biopsies the morphologic changes ensuing over a 6½ months' period after the ingestion of phosphorus. Based upon the serial biopsies obtained from this patient, the findings in the human liver as a result of severe phosphorus poisoning with recovery, consisted of parenchymatous degeneration and fatty metamorphosis of the liver cells in the early stages. This is associated with small areas of focal necrosis of the liver cells and an acute inflammation of the periportal connective tissue. Within 45 days there was no evidence of focal necrosis and there was a decrease in the cytoplasmic degenerative changes. Meanwhile, there was an increase in the inflammatory cell infiltration and lymphocytes replaced the polymorphonuclear leukocytes as the predominant cell.

A progressive increase in the periportal connective tissue occurred. On the 33rd day there was only a slight increase, but on the 86th day the connective tissue extensions from two adjacent spaces had joined each other and produced a "pig" liver lobule. The quantity of tissue obtained at the last liver biopsy, 191 days after the onset of illness, was too small to determine whether this periportal fibrosis was still progressive or whether some regression had occurred.

The lesions seen in the liver biopsy specimens taken from this patient closely resemble those produced by feeding phosphorus to dogs.^{1,14} Cirrhosis appeared in the livers of dogs after a similar interval of time. Further biopsy examinations and studies of this patient will be made at 6 month intervals.

Summary. 1. In the United States most of the deaths due to phosphorus poisoning result from the ingestion of roach paste or fireworks.

2. Patients may die in a shock-like state within 24 hours after the ingestion of yellow phosphorus.

3. Prompt removal of the poison by emesis or lavage is essential to the recovery of patients who have taken a fatal dose of phosphorus.

4. A diet high in protein and carbohydrate and low in fat should be given to protect the liver and the daily fluid intake should be maintained between 3000 and 4000 cc.

5. The anatomic changes in the human liver in acute phosphorus poisoning with recovery showed focal necrosis, fatty metamorphosis and parenchymatous degeneration with acute inflammation of the portal canals in the early phase of illness. The late phase was characterized by periportal connective tissue proliferation histologically compatible with early portal cirrhosis.

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ACUTE MENINGOCOCCAL ENCEPHALOMYELITIS

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It is now recognized that although invasion of the body by meningococci usually results in meningitis, this is not inevitable and other organs may be affected either concomitantly or independently. For example, purpura and cutaneous eruption are so common that the disease has been called spotted fever. The organism most frequently associated with the so-called Waterhouse-Friderichsen syndrome, in which there is massive adrenal hemorrhage, is the meningococcus. Acute meningococcal endocarditis has been occasionally observed. Chronic meningococcal septicemia is a distinct entity and is not infrequent. Meningococcal encephalomyelitis is one of the less common forms of infection; it is given only brief consideration in even the larger textbooks, and only few cases are recorded in the literature. Careful microscopic studies of autopsy material of cases of meningococcal meningitis might not improbably disclose involvement of substances of brain and cord not suspected upon gross examination.

The largest series of cases of meningococcal meningoencephalitis so far reported is that of Banks and McCartney. In a study of 10 cases observed in an epidemic of meningococcal meningitis in England during the winter of 1941-1942, they found several with encephalitis and myelitis. Their analysis of the clinical data showed that in most instances, the involvement of brain and cord can be diagnosed during life.

The following case is reported because (a) there was several unusual features, and (b) it seems well to add to the literature of this disease, so that ultimately a complete description of the disorder can be provided.

Case History. A.W.S., a white male, 27 years old, was admitted to hospital on April 27, 1943, complaining of headache, backache and fever which had been steadily increasing for 24 hours. Just before admission the patient became nauseated and vomited. The past medical history and family history were negative except for one attack of malaria in the autumn of 1942.

On admission, the temperature was 101° F.; pulse, 116; respirations, 15. The patient was acutely ill, vomiting and feverish. The pupils were small,

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reacted normally to light and in accommodation, the reflexes normal. There was questionable stiffness of the neck, which at the time was attributed to the severe headache. The naso-pharynx, chest and abdomen revealed no abnormal signs.

A tentative diagnosis of influenza and possible benign tertian malaria was made.

During the first 2 days headache continued but the vomiting stopped. The clinical impression was that he was improving. However, in the early hours of April 30 he became noisy, irrational, and unmanageable, and was given 10 cc. of paraldehyde intravenously. The spinal fluid was grossly purulent and contained 54,900 leukocytes (mostly neutrophils). There were a few Gram-negative intracellular diplococci which morphologically resembled meningococci. The blood showed 10,550 leukocytes (73% neutrophils; 17% lymphocytes). A diagnosis of meningococcal meningitis was made, and the patient was given intravenously 4 gm. of sodium sulfathiazole (the only available sulfonamide) in 30 cc. of water.

Deep coma developed rapidly. The pupils were small, equal, and reacted to light. The neck was only slightly stiff; Kernig's sign slightly positive. In contrast, there were marked rigidity and orthotonos of the spine; the umbilical and cremasteric reflexes were absent. Knee and ankle jerks were hyperactive but equal, and a bilateral Babinski with fanning was present. No ankle clonus was elicited. Breathing was markedly stertorous, and extreme trismus was present. Five gm. of sulfanilamide were given in 1000 cc. of physiologic saline solution. The breathing became Kussmaul in type, and an alarming pulmonary edema developed despite a strong, full pulse and a blood pressure of 140/85. This edema responded temporarily to oxygen, peripheral tourniquets, venesection, and atropine. At 1 P.M., a cisternal puncture was done in the hope that it would help the dyspnea by lowering intracranial pressure. Although it was not measured, we thought that the cisternal pressure was definitely increased. Five hours later the patient had improved and was given 5 gm. sulfanilamide in 1500 cc. of physiologic saline subcutaneously, as well as 100,000 units of antimeningococcal serum intravenously. In the early evening he became cyanotic and a progressive, severe pulmonary edema developed which failed to respond to any form of therapy, including digitalis intravenously. He died at 2 A.M., May 1, 1943. Cultures of the spinal fluid showed numerous colonies of meningococci which gave characteristic agglutination tests. Cultures of venous blood were negative at the end of 2 weeks. No malaria parasites were found in 4 thick blood films.

The clinical diagnoses were: (1) acute cerebrospinal meningitis due to meningococcus; (2) bronchopneumonia involving the lower lobes of both lungs, etiology undetermined.

PATHOLOGIC EXAMINATION. (Seven hours after death.) The positive findings were confined to the central nervous system and lungs. All other organs were those of a healthy young man. Careful search of specially fixed and stained tissue sections showed no malaria parasites. The pathologic diagnoses were: (1) acute, diffuse, meningococcal encephalomyelitis; (2) acute, purulent, meningococcal cerebrospinal leptomeningitis; (3) edema of brain, marked; (4) confluent bronchopneumonia, all lobes of both lungs, etiology undetermined.

Central Nervous System. The leptomeninges were thin and tightly stretched, and beneath them was a delicate film of creamy, yellow pus, which occupied the Sylvian fissure and the sulci on the lateral and superior aspects of the brain. At the base of the brain, however, and in the cisternæ there was only a small amount of cloudy fluid and no adhesions. The dura mater was hyperemic.

The brain weighed 1550 gm.; the cerebral hemispheres were greatly swollen. The convolutions were broad and flat and almost completely obliterated the sulci. After fixation in 10% neutral formol-saline for 1 week, multiple coronal sections were made of the brain. Numerous clusters of bright red, punctate hemorrhages were scattered throughout the white matter, although the gray matter was mostly spared (Fig. 1). In some places several small hemorrhages

had fused to form larger lesions 5 to 8 mm. in diameter. All the tissues were extremely edematous and hyperemic with wet, boggy, pink cut surfaces. There was no macroscopic thrombosis of the arteries or veins. The ventricles were of normal size and contained thin, cloudy fluid; but there were neither adhesions nor obstruction of the aqueducts. The choroid plexus was covered with fibrinous exudate.

The leptomeninges of the spinal cord contained an increased amount of cloudy, watery fluid, but there were no pockets of pus or adhesions. The pachymeninges were hyperemic. Throughout the white matter of the entire spinal cord were numerous small hemorrhages similar to those in the brain.



FIG. 1.—Coronal section through the region of the thalamus to show the multiple hemorrhages in the white matter of the brain.

Respiratory System. The right lung weighed 900 gm. and the left lung 800 gm. The entire pleura in both thoracic cavities was covered with a layer of yellowish gray, granular, fibrinous exudate. The lungs cut easily and large amounts of cloudy, reddish gray fluid, containing almost no air, flowed from the cut surfaces. All parts of the lungs were extensively consolidated, except for a few small foci at the apex and along the lower margin of the upper lobes. The tissues were pale reddish gray, finely granular, moderately friable and remarkably uniform, so that the pneumonic lesions appeared to be everywhere of the same age. Frothy, red fluid filled the bronchi, but the mucosa appeared to be hyperemic only. The trachea, larynx and nasopharynx were not affected. The pulmonary arteries and veins were normal. The lymph nodes at the hilum were moderately enlarged, and the cut surfaces were bulging, moist, and reddish gray.

MICROSCOPIC EXAMINATION. Technique. Portions of cortex and white matter were taken from the cerebral hemispheres, basal ganglia, pons, medulla oblongata, cerebellum and spinal cord, fixed in 10% formol-saline, embedded in paraffin, cut at 5 μ , and stained with hematoxylin and eosin, van Gieson's and Verhoeff's stains, Mallory's phosphotungstic acid hematoxylin and Goodpasture's bacterial stain. Frozen sections cut at 20 μ were stained for myelin (Spielmeyer) and fat (Sudan III).

Meninges. The cerebral leptomeninges were moderately distended by exudate, which extended into the sulci and for a short distance among the large blood-vessels. This exudate consisted of fluid, much fibrin, and many neutrophils. Lymphocytes, large mononuclears and phagocytes containing

dead leukocytes and cellular débris were present, but there was no organization. The meningeal vessels were strikingly hyperemic, but no thrombi were seen. The dura mater was not affected. The spinal leptomeninges were less diseased; here the exudate was comprised largely of lymphocytes and large mononuclears with only small numbers of neutrophils and little fibrin (Fig. 2).

Brain. The principal lesions were: (1) acute hemorrhagic foci or purpura of the brain and (2) a true acute encephalitis with necrosis. In some regions they occurred in pure form; in others there was a mixture of the 2 types.

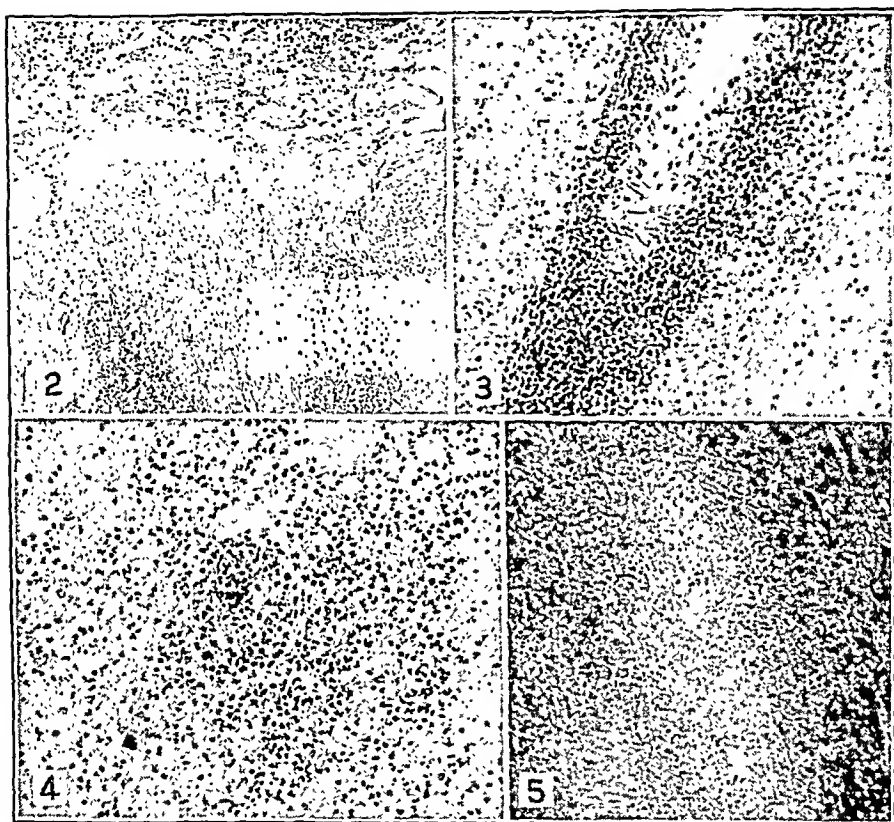


FIG. 2.—Two hemorrhagic lesions in the lateral funiculi of the spinal cord. Note the slight inflammation of the meninges. (Hematoxylin and eosin; $\times 200$.)

FIG. 3.—Perivascular exudation of neutrophils in the cerebral white matter. (H. and E.; $\times 450$.)

FIG. 4.—An area of acute necrotizing inflammation in the white matter of the brain. (H. and E.; $\times 500$.)

FIG. 5.—Area of pallor around a hemorrhagic focus showing displacement of the myelinated nerve fibers by red blood cells. There is no primary demyelination. (Spielmeyer's myelin stain; $\times 100$.)

The hemorrhagic lesions were small foci of recent bleeding scattered widely throughout the white matter of the brain and spinal cord. For the most part the foci were poorly defined and bore no apparent relationship to the arteries or veins. Instead, they were usually situated at some distance from the arteries; they were observed in purest form in the spinal cord (Fig. 2), and in the tissue just adjacent to the lateral ventricles. In other places they occurred either alone or in combination with foci of true encephalitis. The smallest hemorrhages, presumably the freshest, consisted of well preserved erythrocytes, but in the larger ones the red blood cells had undergone conglutination, lysis and a peculiar coagulation necrosis, so that the individual cells were no

longer recognizable. In the relatively few instances where the hemorrhage was perivascular, the earliest change was filling of the affected vessel, often a small artery or arteriole, by conglutinated red blood cells followed by extravasation of erythrocytes into the Virchow-Robin spaces; when these spaces became greatly distended, bleeding into the brain substance took place.

The acute encephalitis was of 2 types, usually quite distinct, although occasionally mixed. These were: (a) perivascular exudation; and (b) focal inflammation and necrosis of the white matter. The perivascular exudation was conspicuous, being present around both small and large vessels (Fig. 3). The exudate was made up mostly of neutrophils with occasional lymphocytes and large mononuclears, some of which were phagocytes, and small amounts of fibrin. The striking feature of the perivascular lesion was its tendency to remain localized in the space of Virchow-Robin (Fig. 3), which was not only true in solitary lesions but also in many of the places where there was diffuse necrotizing inflammation. In a few places, on the other hand, the inflammation around the arteries fused with the surrounding encephalitis, indicating spread from the vessels to the adjacent white matter.

The second manifestation of the encephalitis was widespread and severe necrotizing inflammation (Fig. 4). This varied from small foci, in which degeneration and early necrosis of the white matter had occurred, to large areas of marked brain necrosis and inflammation. Loss of tissue was often great with resulting condensation of nuclei and a highly cellular appearance. All degrees of nuclear change were observed, including karyorrhexis, pyknosis and dissolution of nuclei. Swelling and chromatolysis were common and when the ganglion cells were affected, bizarre multinucleated forms were encountered. Ameboid microglial cells and neutrophils were present in large numbers.

Many of the small arteries, arterioles and capillaries of the brain contained thrombi of coagulated protein material and conglutinated red blood cells, which often showed a peculiar coagulation necrosis. There was no demonstrable injury to the arterial wall, and the exudate was entirely perivascular.

Sections stained for myelin showed numerous areas of pallor corresponding to the areas of hemorrhage and encephalitis. Careful study of these lesions and comparison with sections stained by other methods showed that the pallor was due to displacement of the nerve fibers by extravasated erythrocytes and inflammatory cells and not to primary demyelination (Fig. 5). Individual nerve fibers could be traced into the pale areas where they were either broken or pushed to one side by the hemorrhage or exudate. It was simply a case of nerve tissue being displaced by other cells.

In the spinal cord the lesions were hemorrhagic. Necrosis and exudation were not observed, and there was no primary demyelination.

DISTRIBUTION OF LESIONS. Hemorrhagic as well as inflammatory lesions were found throughout the white matter of both cerebral hemispheres. They were most common in the posterior frontal, parietal and anterior occipital regions. The corpus striatum, thalamus and mid-brain were not as markedly involved and only occasional lesions were found in the medulla oblongata, pons and cerebellum. Inflammatory and mixed type lesions predominated in the white matter surrounding the thalamus and corpus striatum, whereas hemorrhagic lesions were most conspicuous in the frontal and occipital lobes.

The cerebral cortex was largely spared, except for chromatolysis of the pyramidal cells and swelling of the oligodendrial cells. The microglial cells were mostly normal.

The choroid plexus was the seat of an acute purulent inflammation similar to that present in the leptomeninges.

In the spinal cord, throughout its length, hemorrhagic lesions were indiscriminately scattered through the three funiculi of the white matter. The lateral funiculi were particularly affected.

Respiratory System. There was widespread confluent bronchopneumonia, which affected nearly all the pulmonary parenchyma. In contrast to the gross appearance, which was remarkably uniform, the microscopic picture varied considerably. The exudate contained great numbers of neutrophils and small numbers of mononuclears. Fibrin was scanty, was seen in only a few places

and there was no organization. Edema was conspicuous, especially in areas where the pneumonia was spreading, hyaline membranes lined many of the alveoli. Passive hyperemia was marked. The bronchi and bronchioles were plugged with exudate, with inflammation spreading into the surrounding tissues. No hyaline membranes were found in the bronchi, and there was only an occasional focus of necrosis of the lining epithelium. Bacterial stains showed no organisms, but in cultures of the lungs a few colonies of non-hemolytic *Staphylococcus aureus* and *Streptococcus faecalis lactis*, grew but no meningococci were found.

Discussion.—The striking clinical observations were: the sudden onset of meningitis in a patient thought to be recovering from a mild upper respiratory infection; the fulminating course of the disease; the rapid development of deep coma and stertorous respiration; the marked pulmonary edema which failed to respond to treatment; and the absence of signs of pulmonary consolidation until shortly before death. At autopsy, the inflammation of the meninges was much less than had been anticipated and was certainly not sufficient to have caused death. The noteworthy and unexpected finding was the presence of a widespread, hemorrhagic and necrotizing encephalomyelitis, limited chiefly to the white matter. Confluent bronchopneumonia involved all lobes of the lungs and was of much greater extent than had been supposed from clinical signs. There was no disease of the adrenals.

This case corresponds to those reported by Banks and McCartney,¹ who divided their 10 cases of meningococcal encephalitis into 3 groups on the basis of clinical and pathologic observations. In the first, fulminating encephalitis predominated with signs of purpura, coma, cerebral edema, widespread punctate hemorrhages, capillary thrombosis, and no cellular exudates. Meningitis was absent or minimal. In the 2nd group, cases of acute encephal meningitis, patients either died within a few days or recovered with transient Parkinsonism. Clinically, the picture was of acute meningitis, complicated by encephalitis (coma, cyanosis, and stertorous, rapid, irregular respiration). Pathologically, there was either hyperemia, hemorrhage, and capillary thrombosis; or an acute exudative inflammation. The 3rd group was chiefly meningitis with focal encephalomyelitis. Occasional massive adrenal hemorrhage was found, but was different from the acute meningococcal infection which involves the adrenal but not the cerebrum or the meninges.

On the basis of both clinical and pathologic features, our case falls into the 2nd group described by Banks and McCartney. The only differences are that myelitis was an important finding, and that there was an extensive pneumonia. Banks and McCartney hold that meningococcal encephalitis is seen most frequently either at the height of an epidemic, when the organisms supposedly are highly virulent and the dose massive; or, in non-epidemic times, at the period of greatest prevalence of the disease. Yet, the present case occurred when there was no epidemic, and in the early autumn, when meningitis was not prevalent.

It is interesting to note that in most of the reported cases 2 distinct lesions have been found in the brain, *viz.*, hemorrhagic and inflammatory. These are seen in pure form as well as in combination. The

reasons for this are not known, but it may be that the hemorrhagic lesions are the counterpart in the brain and spinal cord of the cutaneous rash and purpura, as well as of the adrenal hemorrhage seen in Waterhouse-Friderichsen syndrome.

Myelin sheath stains showed that, although necrosis and displacement of brain tissue produced zones of pallor in the myelin preparations, true demyelination did not occur. The absence of demyelination distinguishes this disease from the cases of acute hemorrhagic leuko-encephalitis of Hurst³ and other rare, primary demyelinating diseases.

The etiology of the pneumonia is not established. It may, of course, have been caused by meningococci; but these organisms were not cultured from the lungs, and could not be demonstrated in bacterial stains of the tissues. Even if meningococci had been isolated, the diagnosis would not have been established, for, in the presence of meningococcal septicemia, the organisms might be cultured from almost any organ. Probably it was a post-infectious pneumonia of some sort, similar to the post-influenzal pneumonias. The rapid development and spread is most likely explained by the marked pulmonary edema which provided both a suitable culture medium and an excellent vehicle for dissemination.

Summary.—This is the report of the case of a young soldier who by clinical examination and laboratory tests appeared to have acute meningococcal cerebrospinal meningitis, with deep coma, difficulty in breathing and extreme pulmonary edema. At autopsy, however, he was found to have had acute encephalomyelitis, violent and extensive, with but comparatively little meningitis. The encephalitis was characterized by purpura of brain and cord and acute necrotizing exudative inflammation, but no demyelination. The case is like those described by Banks and McCartney, but differs in that it did not occur during an epidemic nor at a time when meningitis was prevalent.

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A MUMPS EPIDEMIC IN A SMALL TASK FORCE

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THIS paper presents a study of a mumps epidemic which occurred in a small Task Force during 1942-1943. Most of the cases were contracted enroute to, and after arriving at, a tropical overseas base. A number of cases occurred in the United States while the Force was in training, but the hospital records of these cases were not available for study. Consideration is given to the effect of variations in housing and

environment upon the spread of the disease; certain clinical manifestations of mumps as it occurred in this Unit are also described.

The elements of this Unit were activated in Louisiana in February, 1941. The first mumps case appeared there in early autumn, and, thenceforth, the hospital was almost never without a case of mumps. The spread of the disease was never remarkable, remaining solely in one company. This isolation is probably explained by the mild weather prevailing in Louisiana and by the fact that troops were housed in tents holding only 4 to 6 men. In February, 1942 the battalion was transferred to another camp. There, the men lived in two-story barracks housing about 65. The number of buildings was inadequate, and crowding was the rule. The weather, too, was generally unfavorable with a coincidental high rate of respiratory infection. At that time an increase in mumps cases was noted; but after consultation with the Camp Medical Inspector, it was decided that no especial precautions need be taken.¹ From April to October, 1942, 22 cases of mumps appeared, mostly from the original focus, Company "A," with 3 cases each developing in Company "B" and Company "C," and 1 in another unit of the Force. One case of German measles occurred, but there were no subsequent cases. In October the Force was transferred, temporarily to a third camp, where, in 3 months, 8 more cases of mumps appeared, strangely enough all in Company "D." Again it is pointed out that this was a period of respiratory infection prevalence.

The final move of the Force was to a Port of Embarkation; and in 2 weeks there, 10 more cases of mumps developed. Whatever individuality the components of the Force had prior to this move was now lost. All Units dined in a common mess hall and, in addition, attended lectures and training films *en masse*. The mixing of troops was further exaggerated during the movement overseas when overcrowding of men became an unfortunate necessity. It was not unexpected, therefore, that an explosive outburst of new mumps cases occurred widely, and, in the following month, a total of 54 cases appeared. Subsequently 28 were transferred to the station hospital, and these, plus 101 others which developed after debarkation, constitute the basis of this report proper.

Incidence. Chart 1 depicts the course of the epidemic and correlates the number of cases with environmental conditions. It is evident that the greatest incidence of cases is closely associated with the inclement weather and overcrowding. At the overseas base, housing conditions were good; there was no crowding; and barracks were constructed to permit four-way ventilation. The climate was favorable during the early months after arrival, and exceptionally few respiratory complaints were noted on sick call. The number of mumps cases reached a peak during the first month after arrival and then precipitously died away.* In a random sampling, 381 men admitted having mumps previously, 187 denied having had mumps, and 13 were doubtful. Why these susceptible men did not contract the disease is conjectural; but it is

* Contact with the local population was not close. To our knowledge, only 1 native contracted mumps.

known that mumps antibody can be demonstrated by complement-fixation tests even without a history of obvious infection.² Also, adequate ventilation of barracks may have played a large part in stopping the spread of this infection.⁷

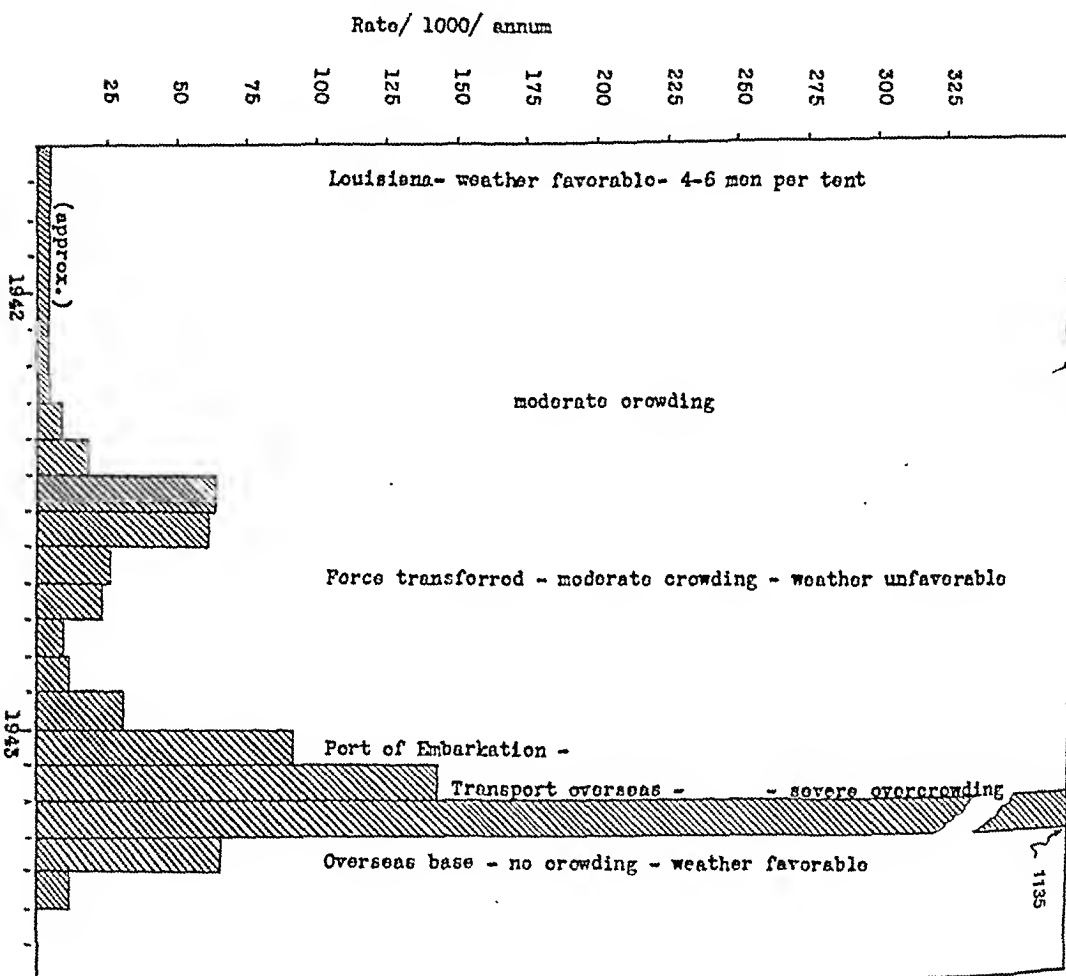


CHART 1.—Incidence of mumps correlated with season and housing of troops.

In this series of 129 cases (126 males and 3 females), the total number of days lost was 2657, which represents a staggering figure, but in keeping with previous experience with mumps in the Army.^{5,6} The average hospital days from all causes was 20.2; from mumps and complications referable to it, 19.3 days (102 cases); and from mumps uncomplicated 18.2 days (30 cases).*

The average age of all patients was 24.8 years. Nine men were over 30 years of age.

Eight cases (6%) claimed definitely to have had mumps before, and 2 of these initial attacks occurred under our own observation. One,

* It must be remembered that these figures do not represent days of actual illness, but the time hospitalization was deemed necessary to cover at least the minimum period of infectivity in each case.

treated for bilateral mumps without complication in July, 1942, developed bilateral mumps again in March, 1943, this time with a complicating unilateral orchitis. The 2nd case had bilateral mumps on March 20, 1943 and developed left parotitis on May 14, 1943.⁹

Clinical Manifestations and Course. Few cases presented prodromata. Only 14 of the 129 cases had prodromal complaints, mostly minor and lasting from 1 to 3 days. Six had headaches; 4, sore throat; 2, malaise; 2, abdominal pains; 1, earache; and 1, nasopharyngitis. However, 1 patient was admitted as a malaria suspect, complaining of headaches, fever, chilly sensations, weakness and infrequent cough.* His temperature was 101.8° F.; the leukocyte count, 10,100 (41% lymphocytes). Blood smears for plasmodia were repeatedly negative, and, after 2 days, bilateral parotid pain and swelling established the true diagnosis. Another case was admitted with a temperature of 102.8° F., chills, weakness and severe headache. Malaria, typhoid fever, and atypical pneumonia were considered; and, though chest examination and Roentgen rays were negative, sulfathiazole was given (indication?). Two days later left parotitis became evident. The leukocyte count was 10,000 with 55% lymphocytes.

There was little difficulty in diagnosis. The great majority of cases reported with established parotid swelling; while others, without this, gave a typical story of "my jaw locked" or complained of pain and/or tenderness over the angle of the jaw. Four patients were admitted with testicular complaints alone, and 3 of these, subsequently, developed parotitis. The 4th never presented definite parotid involvement and is included as a mumps case on the basis of the prevailing epidemic, bilateral orchitis, absence of venereal disease or inguinal lymphadenopathy, and a leukocyte count of 7300 with a relative lymphocytosis of 58%.

Uncomplicated mumps ran a smooth course. However, 44† (35%) of the 126 males in this series developed orchitis 6 days, on an average, after the initial complaint. This incidence is higher than the usual 15 to 30% found in other series.^{3,8} Physical trauma to the testes has long been accepted as an exciting cause of mumps orchitis. However, strict bed rest alone has been shown not to lower the incidence.⁴ Prophylactic support to the testes was done on a few cases, and the impression was that it did not help. This command has consistently had a high venereal disease rate, and the point was raised whether or not the trauma resulting from a gonorrheal infection might lower local tissue resistance and thereby predispose to orchitis. Although a previous epididymitis would be a pertinent factor on which to base conclusions, it was found too difficult to obtain this information; and, instead, a previous history of gonorrhea alone was used. Of the 126 males in this series, a positive history of gonorrhea was given by 54 men. The incidence of orchitis in this group was 31%, while the incidence in those denying previous gonorrhea was 37%. Thus, pre-

* Malarial fever, estivo-autumnal, is hyperendemic at this Post and experience has taught us to suspect malaria in all cases until proven otherwise.

† Includes 1 case of bilateral orchitis without parotitis.

vious gonorrhea may be ruled out as a predisposing factor in mumps orchitis.*

TABLE 1.—GONORRHEA AND THE INCIDENCE OF MUMPS ORCHITIS

	Cases	No. developing orchitis
Previous history of gonorrhea	54	17 (31%)
No previous history of gonorrhea	72	27 (37%)

Orethritis rarely occurs before puberty, which suggests that age may play a part in etiology. The mumps cases were divided, therefore, into those younger than 25 and those older (the average age in the series was 24.8 years). Of the 126 males, 79 were in the younger age group, and 32 (41%) of these developed orchitis. Forty-seven men were in the older age group, and 12 (26%) developed orchitis. Thus, age does not predispose to the development of this complication; and, if any conclusion may be drawn, the younger (more active?) adult seems more disposed.

TABLE 2.—AGE AND INCIDENCE OF MUMPS ORCHITIS

Age	Cases	No. developing orchitis
Under 25	79	32 (41%)
Over 25	47	12 (26%)

Of the 44† cases with orchitis, 25 developed in patients presenting bilateral mumps and 18 from cases of unilateral mumps. Of the 18 cases with unilateral parotitis, 4 developed bilateral orchitis. Of 25 cases with bilateral parotitis, 9 developed bilateral orchitis. This suggests that bilateral parotitis tends to a slightly greater incidence of bilateral orchitis.

TABLE 3.—COMPARISON BETWEEN UNILATERAL AND BILATERAL PAROTITIS IN RELATION TO EXTENT OF SUBSEQUENT MUMPS ORCHITIS

Unilateral parotitis:	
Unilateral orchitis	14
Bilateral orchitis	4 (22%)
Bilateral parotitis:	
Unilateral orchitis	16
Bilateral orchitis	9 (36%)

Six months after recovery, the 44 patients who previously had orchitis received a follow-up examination. Testicular atrophy was noted in 21 (48%), and varied from slight to moderate in degree.

Other complications referable to mumps were: 1 meningo-encephalitis (Case 1) and 1 questionable pancreatitis.

Intercurrent diseases occurred in 28 patients. It included 8 cases of malaria (Case 2), 4 gonorrhea, 3 bronchitis, 3 conjunctivitis, 2 chancre, 2 nasopharyngitis, 2 tonsillitis, 2 myositis, 1 balanitis, and 1 appendicitis (Case 3).

The average highest temperature in this series was 101° F. Two cases had temperatures of 105.2° F., both with complicating malarial fever. One case each of mumps meningo-encephalitis, bronchitis, and gonorrhea developed 104.8° F.; 27 cases developed temperatures of

* However, all 4 men with intercurrent acute gonorrhea developed orchitis.

† Includes 1 case of mumps orchitis without parotid involvement.

103° F. and higher, with 16 referable solely to mumps; 20 cases had temperatures ranging between 100° and 103° F.; 13 cases showed no elevation in temperature at any time; the majority of cases had temperatures between 98° and 100° F.

Laboratory Data. The average leukocyte count for all cases was 6520 per c.mm.; for the cases presenting intercurrent disease, 7500; and for mumps and complications referable to it, 6210. The highest leukocyte count in this series, 36,000, occurred in the case with intercurrent appendicitis; however, the next two highest counts, 10,250 and 10,100, occurred in cases of uncomplicated mumps. The lowest leukocyte count was 3600.

Lymphocytes averaged 36% in all cases and ranged from 15% to 59%. Only 4 cases showed lymphocytes below 26%, while 5 cases were above 50%.

All urinalyses were negative, except 3. Two showed traces of albumin which accompanied temperatures of 103.2° F. and 104° F. and are considered as febrile albuminuria; the 3rd showed a trace of albumin and a few red cells, but follow-up urinalyses were always negative.

Treatment. Treatment was symptomatic in all cases with results satisfactory throughout the series. Sulfathiazole was given in 8 cases for various indications, and there appeared to be no change in the usual course of mumps or in the incidence of orchitis. This agrees with a conclusion reached in a larger study.³ None of the orchitis cases was treated surgically.

Report of Cases. CASE 1. Male, aged 25, admitted March 23, 1943 with a complaint of pain of 1 day's duration involving both sides of the face. Past history and family history were non-contributory. Physical examination was normal except for injection of the oropharynx and ostium of left Stensen's duct. Both parotid areas were tender, but no swelling was discernible. Blood study showed: red blood cells, 5,820,000; hemoglobin, 95%; leukocytes, 4250 with 47% lymphocytes. Urinalysis was negative. A diagnosis of mumps was made; and, in a few days, pain and tenderness disappeared completely.

On March 29 the patient complained of severe frontal headache. The temperature was 102° F. and pulse rate, 92. Acetyl salicylic acid and an ice-bag afforded no relief. The temperature rose to 102.4° F., and later to 104.8° F. The pulse rate varied from 80 to 120 and at times was disproportionately slow in relation to the temperature. Slight nuchal rigidity was found which progressed rapidly to complete head retraction and opisthotonos. An occasional convulsive spasm shook the patient and once there was a momentary chill. Projectile vomiting occurred twice within a few hours. Restlessness and delirium became manifest. Neurologic examination revealed the presence of Kernig, Brudzinski and Babinski signs. The superficial reflexes were exaggerated and the deep reflexes diminished. The impression was mumps meningo-encephalitis, but serious consideration was given to the possibility of malarial fever, cerebral type. Repeated negative blood smears for plasmodia ruled out the latter possibility. A spinal tap was done, withdrawing 15 cc. of clear, colorless fluid under some increased pressure. The fluid showed no organisms or pleocytosis. The Pandy test was negative. A leukocyte count was 5750 with 34% lymphocytes. The following day, a repeat blood count showed 3750 leukocytes with 58% lymphocytes.

The patient's condition appeared grave, but the spinal tap seemed to relieve him. Sulfathiazole was given empirically, 2 gm. initially and 1 gm. every 4 hours thereafter, in addition to symptomatic treatment. Within 2 days, all abnormal neurologic findings had disappeared and, except for an infrequent

headache and emesis, the patient went on to a complete cure, with discharge to duty on April 15.

CASE 2. Male, aged 33, admitted March 21, 1943, complaining of pain in the right side of the face of 4 day's duration and slight local swelling for 1 day. Physical examination was negative, except for slight swelling, and marked tenderness of both parotid areas. With symptomatic care, the parotitis subsided within a few days. There was no fever at any time.

On March 28 the patient had a temperature of 100° F. and a slight headache. The temperature rose to 105° F. on March 29. Malaise and severe frontal and occipital headache were present. No relief was obtained from ice-caps or repeated doses of acetyl salicylic acid. Beginning mumps meningo-encephalitis was suspected, but neurologic examination at this time was entirely normal. On March 30 slight meningismus and absent cremasteric reflexes were noted, and sulfathiazole therapy was begun empirically. Slight epistaxis occurred 4 times within 48 hours and non-projectile vomiting twice. Lumbar puncture was done, withdrawing 25 cc. of clear, colorless fluid under an initial pressure of 18 mm. of mercury. No bacteria, pleocytosis, or increased albumin were found. A blood count showed: erythrocytes, 5,140,000; leukocytes, 6200; neutrophils, 72; eosinophils, 2; basophils, 1; and lymphocytes, 25. A thick-film blood smear revealed *P. falciparum*, 125 rings per 100 white cells.

Antimalarial treatment was started immediately and sulfathiazole was discontinued. The following day, the patient felt better but continued to suffer an occasional headache for 4 days. The temperature returned to normal on the 5th day, and the patient was discharged from the hospital on April 20, as cured.

CASE 3. Male, aged 23, admitted March 19, 1943, with a complaint of pain, tenderness, and swelling of the right parotid area. Examination was negative, except for the local findings. By March 23, all complaints had cleared.

On March 25 the patient developed abdominal pain, so severe as to demand morphine. Diarrhea was also present and emesis occurred later. The pain began in the right testicle and radiated toward the umbilicus. The testicle was not enlarged but was slightly tender. Abdominal tenderness was most marked in the right suprapubic region. There was no rigidity or rebound tenderness. Attempts to extend the right leg increased the pain. Temperature and pulse rate were normal and a blood count showed: 16,300 leukocytes; neutrophils, 83%; lymphocytes, 17%. A later blood count showed: 20,100 leukocytes; polymorphonuclears, 85%. Urinalysis was negative throughout.

The next morning, temperature and pulse rate were still normal, and a blood count showed: 22,300 leukocytes; neutrophils, 87%. Pain and tenderness were now most marked along the course of the right spermatic cord and lateral to the usual site of the appendix. The pain was more intense than usual in appendicitis. Because of these findings and the recent mumps, a diagnosis of early orchitis with reflex pain along the spermatic cord was considered most likely. However, serious consideration was given to a diagnosis of acute appendicular obstruction, and close observation was continued. That afternoon, the temperature rose to 101.4° F. An erythrocyte sedimentation rate (Wintrobe) was 24 mm. in an hour, and another blood count showed: 36,000 leukocytes; and, polymorphonuclears, 82%. The pain had eased slightly and was now localized in the right lower quadrant. Nausea was present. Examination now showed right rectus spasm, tenderness, and rebound tenderness in the right lower quadrant, maximum over McBurney's point. In view of this new picture, immediate operation was advised.

Acute, suppurative appendicitis was revealed on operation. A fecalith, the size of a date seed, was found impacted at the base of the appendix and the entire organ was inflamed, swollen, and tense, with rupture imminent. The tip was adherent to the lateral wall, which accounted for the atypical location of the early findings. Appendectomy was performed, and, after an uneventful convalescence, the patient was discharged to duty on April 21.

Summary and Conclusions. 1. A history of a mumps epidemic in a small Task Force is described.

2. The total days lost by hospitalization in the series of 129 cases was 2657. This is a large figure, but is in keeping with previous experience with mumps in the Army.

3. A correlation is evident between inclement weather and crowded living conditions and the incidence of mumps.

4. Few cases presented prodromata, and diagnosis was obvious in the great majority.

5. Orchitis developed in 35% of this series. Neither age nor a history of previous gonorrhea appeared to play a part in the incidence of this complication. One case of mumps meningo-encephalitis and one of mumps orchitis without parotitis occurred.

6. Leukopenia, with a relative lymphocytosis, was present in most cases. Urinalysis was uniformly negative.

7. Treatment was symptomatic with satisfactory results. In 8 cases, sulfathiazole was given and seemed not to affect the course of the mumps.

8. Of 129 cases, 3 are reported in some detail.

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PROGRESS OF MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF

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THE USE OF PENICILLIN IN SURGICAL INFECTIONS

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SINCE penicillin is a powerful chemotherapeutic agent which has a specific effect on the organisms responsible for the majority of infectious lesions commonly classified among surgical diseases, it is becoming apparent that the treatment of many of these diseases may require radical revision. However, there are certain pathogenic bacteria against which penicillin, in concentrations obtainable *in vivo*, is not effective, including the gram-negative bacilli, some of the non-hemolytic streptococci and occasional strains of staphylococci. Thus certain limitations of the drug are already clearly defined. Adequate supportive therapy remains an essential feature in the management of surgical infections and should include operative intervention when indicated.⁸

There have appeared in recent months many reports on the use of penicillin in a variety of infections, although few of them have included enough cases to allow statistically significant deductions to be made. Generally, cases have been classified in terms of their etiologic organisms, for the decision as to whether or not a patient should receive penicillin has depended upon the causative organism and its susceptibility to the drug. Early workers with penicillin showed that the drug is a potent chemotherapeutic agent capable of inhibiting most gram-positive organisms and gram-negative diplococci.^{2,7,12} They further demonstrated the lack of effect upon gram-negative bacilli. Abraham and Chain,¹ working with *Escherichia coli*, found that these and other gram-negative bacilli produce a substance which rapidly destroys the bacteriostatic activity of penicillin. They called this substance penicillinase.

Dosage and Administration. Many points of controversy have arisen since penicillin has been available but, because of the limited supply,

* Now on Active Service in the Armed Forces.

considerably more experience is necessary before they can be conclusively settled. Paramount among these is the question of dosage, which has been heavily influenced by the inadequacies of supply. Because of this, minimal, rather than optimal, amounts have been recommended.

The daily dosage recommended by investigators varies from 40,000 to 400,000 Oxford units.^{5,11,21,28} The fact that penicillin is a relatively non-toxic drug^{7,37} will probably result in the use of larger doses as supplies increase.

Severe staphylococcal sepsis requires the largest doses among the surgical infections.^{5,28} The majority of investigators recommend a total 24-hour dose of approximately 100,000 units;^{11,21,25} however, Lyons²⁸ and Bloomfield *et al.*⁵ suggest the use of considerably larger amounts, 200,000 to 400,000 units for the initial therapy. The average range of recommended dosage for other surgical infections varies from 40,000 to 150,000 units per day, although Lyons²⁸ expresses the view that the treatment of clostridial infections may require a dosage exceeding 400,000 units per day. Mixed bacterial infections which frequently contain saprophytic gram-negative bacilli do not appear to respond as promptly or as uniformly as infections yielding pure cultures.¹¹ Larger dosage may be required to bring these lesions under control.

Since it is possible to demonstrate *in vitro* that organisms growing in low concentrations of penicillin may develop fastness, it appears that adequate initial therapy to obtain a rapid response is indicated.⁵

The clinicians working with penicillin agree that the administration of continuous intravenous infusions of the drug is indicated in all severe infections in which the mortality is high. Herrell^{20,21} has demonstrated that a low dosage is more efficient if given by continuous infusion, and has utilized this route of administration throughout the course of treatment in many of his cases. Others feel that the intramuscular route of administration is preferable after the patient has made a satisfactory response to the initial intravenous therapy.^{5,11,25,28} Besides the technical difficulty encountered in maintaining any continuous infusion into a vein, there is the troublesome feature of venous thrombosis at the site of injection which not only complicates administration, but may be quite painful. Herrell's²¹ experience with venous irritation from glucose solution seems justified; however, it is impractical to use isotonic saline solution exclusively for fear of producing disturbances in electrolyte balance. Alternating diluents of normal saline and 5 per cent glucose in distilled water have been used most successfully. The size of the needle, its insertion into the vein, and the length of time a vein is used are all important features of technique. It has been recommended that 18-gauge needles inserted up to the hub in a fresh vein each day be used. After determining the amount of intravenous fluid a patient can tolerate, the daily dosage should be dissolved in this amount of fluid so that the rate of administration is constant.

For all patients who need systemic therapy and who do not require intravenous treatment, the use of intramuscular injections every 2 to 4 hours is commonly used. The more frequent injections may be preferable.¹⁵ It is wise to use the larger muscle masses, rotating injections from one part to another to assure complete absorption and to avoid repeated local trauma.²⁵

If intravenous therapy is indicated, and if for any reason veins are not available for venepuncture or cannulization, bone marrow infusions may be used according to the technique of Tocantins.⁴⁰

The use of local therapy will be included under individual headings.

Lt. G. F. Schmidt³⁸ adequately reviewed the literature on the pharmacologic properties of penicillin and the types of toxic reactions in the May, 1944, issue of this journal.

Acute Infections. BACTEREMIA. *Staphylococcal.* Penicillin is the most effective agent available for the treatment of staphylococccemia. The mortality from this disease prior to the use of sulfonamides was about 85%. With sulfonamide therapy the mortality was reduced to about 70%. In the report of Kccfer *et al.*²⁵ in August, 1943, the mortality in 91 cases treated with penicillin was 37%, but this series included patients who were inadequately treated during the early trials of this new drug and 9 cases of acute staphylococcal endocarditis in which the mortality continues to be high. Lyons²⁸ later reported 9 cases with 3 deaths. More recently, Dawson and Hobby¹¹ published a series of 18 cases with a mortality of 16.7%, and Herrell²¹ reported 14 cases with only 2 deaths (14.3%). These latter figures should give a more adequate answer regarding future mortality in staphylococccemia with the use of penicillin.

Any patient with staphylococcal bacteriemia should receive adequate penicillin therapy at the earliest possible moment and preferably by continuous intravenous infusion.^{5,11,21,25,28} It is important to determine promptly the source of the infection, and either excise or drain it surgically or institute other forms of adequate local therapy as indicated.²³

The rapid subsidence of the severe staphylococcal toxemia after 8 to 72 hours of treatment is one of the most dramatic responses to penicillin therapy.¹⁵ Objectively, patients appear much better even though their temperature and white blood cell count remain elevated. The Floreys¹⁵ have emphasized the importance of following the patient and not the chart. In these and other acute infections, the red blood cell count may be suppressed by the action of toxins on the bone marrow, but with inhibition of the parasitic organisms and the subsequent elimination of toxicity, the bone marrow will often respond to demands. Florey and Florey reported several cases in which there was a rapid rise in the hemoglobin following the institution of penicillin therapy.¹⁵ This, of course, does not exclude the use of blood transfusions when indicated.

Acute Hematogenous Osteomyelitis. Acute osteomyelitis is commonly associated with bacteremia, even though positive blood cultures may not always be obtained. The mortality in acute staphylococcal osteomyelitis is considerably lower than that in staphylococcal bacteremia resulting from soft tissue foci. With the use of sulfonamides, the reported mortality of this disease has fallen to levels ranging from 0 to 10%. Hoyt, Davis and Van Buren²² reported 8 cases treated with sulfathiazole with no deaths. More recently, Baker, Schaubel and Kuhn⁴ reported 56 cases treated with sulfonamides with only 1 death. Results of treatment with penicillin have not been universally successful, but this is at least partially explained by the fact that initiation of this form of therapy has been only after adequate sulfonamide trial and failure. Due to the greater potency of penicillin the response should be more rapid than with sulfonamides.²

Since the advent of sulfonamides, the practice of early surgical drainage in acute osteomyelitic lesions has been subjected to question. Hoyt, Davis and Van Buren²² first demonstrated the value of aspiration or non-surgical drainage when the sulfonamides were employed. Recently Baker, Schaubel and Kuhn⁴ ran a comparative series of sulfonamide treated cases with surgical drainage and needle aspiration which showed that fewer draining sinuses remained when non-surgical methods were employed. This should also be true with the use of penicillin, which

offers the additional feature of local treatment into the abscess cavity after aspiration.²⁰

Beta Hemolytic Streptococcic Bacteremia. With the use of sulfonamide therapy this disease develops less frequently and results in a lower mortality than staphylococemia. However, the response to treatment may be more prompt with the use of penicillin since comparative *in vitro* studies show it to be more potent than the sulfonamides.¹³ Streptococci are more sensitive to the effect of penicillin than staphylococci which permits adequate clinical response with somewhat lower doses.²⁵ Intravenous therapy is indicated in all types of bacteremias.

SUPPURATIVE INFECTIONS OF NATURAL BODY CAVITIES. *Empyema.* Sulfonamides have lowered the incidence of empyema following pneumococcal pneumonia, but are inadequate in the treatment of pneumococcic empyema since the presence of large numbers of bacteria of pus and tissue autolysates definitely reduce the effectiveness of these drugs.²⁷ Penicillin, on the other hand, is not inhibited by these substances¹⁵ and is the drug of choice in the treatment of pneumococcic, staphylococcic, streptococcic and mixed types of empyemata which do not include a predominance of gram-negative bacilli. After the aspiration of pus, local penicillin instilled into the abscess space may be adequate to control completely the infection without the necessity of systemic therapy if the infection is well localized. By these means it is usually possible to avoid surgical drainage. The daily instillation of 25,000 to 50,000 units of penicillin is recommended.^{25,39}

Tillett, Cambier and McCormack³⁹ have reported success in 1 case of pneumococcic empyema following a single instillation; however, 5 to 10 days of treatment is usually required. The pus is frequently sterile after the first or second administration of the drug and subsequently becomes thinner and decreases in amount. The accumulation of thick fibrinous material may necessitate thoracotomy.²⁵ The response to treatment of empyemas with mixed flora has been considerably slower than in those cases which yield a pure culture. Penicillin should not be used as an irrigating solution in empyema since 6 to 8 hours' contact is required to obtain bacterial stasis.²⁵ If irrigation is to be performed, it is best done with normal saline. With open surgical drainage of an empyema cavity the usefulness of penicillin sharply decreases since it tends to leak through the wound. If possible, it is wise to avoid surgical drainage.

Suppurative Arthritis. Acute staphylococcic, streptococcic, gonococcic, pneumococcic and meningococcic suppurative arthritis should be treated in the same manner as empyema. Systemic therapy is not required unless there are other active foci. The dose required is small, 5000 units instilled after aspiration being adequate.²⁵

Meningitis. Secondary suppurative meningitis caused by pneumococci, staphylococci and streptococci should receive penicillin systemically and locally instilled into the spinal fluid.²⁵ Rammelkamp and Keefer³⁶ demonstrated the failure of penicillin to appear in the spinal fluid following systemic administration. This work has been further established by Pilcher and Meacham.³³ These infections should be considered surgical, as they are most frequently secondary to suppurative lesions located in the mastoids or paranasal sinuses. Every attempt should be made to drain these cavities of purulent material, after which penicillin solution containing 250 to 500 units per cc. may be instilled into the cavity at frequent intervals.¹⁵ The importance of the use of intracisternal or intraspinal therapy in combination with systemic treatment is clearly apparent.³³

Suppurative Pericarditis. Acute suppurative pericarditis produced by pyogenic cocci should receive systemic penicillin therapy. Surgery may be avoided in some cases by frequent aspiration of pus from the pericardial sac followed by the instillation of 5000 to 20,000 units of penicillin, depending upon the amount of pus removed, and the size of the cardiac shadow on Roentgen ray.

Peritonitis. In peritonitis, penicillin is not usually indicated since penicillinase-producing coliform organisms are generally present.²⁶ In cases in which pyogenic organisms occur without gram-negative bacilli, penicillin may be useful and should be administered both systemically and locally as indicated.

ABSCESSSES. *Carbuncles and Furuncles.* These staphylococcal infections may be aborted in the early stages of development with systemically administered penicillin.¹⁵ But once necrosis has taken place, pus and necrotic tissue should be evacuated by either surgical drainage or aspiration. If aspiration is employed, locally injected penicillin is recommended.²⁰

Visceral Abscesses. These lesions, whether located in the brain, the lung, the mediastinum or other structures, should receive systemic treatment. Liver abscesses usually do not respond to penicillin, since these lesions usually contain coliform organisms. Penicillin is concentrated in the bile,³⁵ which should make it of use in pyogenic biliary tract infections which do not contain penicillinase-producing organisms.

LOCALIZED WOUND INFECTION. *Cellulitis, Lymphangitis and Lymphadenitis.* These infections will usually respond to systemic penicillin therapy. If there is extensive cellulitis and lymphadenitis which results in localized necrosis, surgical or non-surgical drainage is recommended.

Cellulitis of the Face. Septic cavernous sinus thrombosis, periorbital and retro-orbital cellulitis, cellulitis of the nose and cellulitis of the lip usually respond dramatically to penicillin. In septic cavernous sinus thrombosis mortality was almost 100% before the use of sulfonamides with only an occasional recovery.¹⁷ The sulfonamides have reduced the mortality to some degree, but penicillin should be even more effective. These patients should have systemic therapy administered intravenously.²⁵ The use of anticoagulants such as dicoumarin and heparin is recommended as a supportive measure.¹⁷

BURNS. The importance of burns and their care has been accentuated by the frequency of these wounds in modern warfare. It is most important to prevent pyogenic infection in the superficial burns, for they may be converted into deeper wounds resulting from loss of epithelial structures. Gentle cleansing and application of pressure dressings have been established as the local treatment of choice.³ Locally supplied sulfonamides in ointments to burn surfaces have left much to be desired.³² Clark *et al.*⁹ reported in *The Lancet*, 1943, 54 burns and scalds in varying stages of healing which had hemolytic streptococci on their surfaces. These organisms had been particularly troublesome in their burn ward. In 41 cases (76%) streptococci disappeared within 5 days with the use of penicillin in a Lannette Wax cream base applied to the surface. All cases showed some improvement. Staphylococci, likewise, disappeared quickly. No toxic effects were noted. *E. coli*, *B. proteus* and *B. pyocyaneus* were not affected. Keefer *et al.*²⁵ recommended the use of locally applied penicillin to prepare granulation surfaces for grafting. Bodenham⁶ reported that streptococci are present in 30 to 80% of the cases he had seen. *Staphylococcus aureus* was present in 100%. He used penicillin in a Lan-

nette Wax cream base as an ointment and in combination with sulfanilamide as a powder. By the use of the cream preparation it was possible to eliminate streptococci and staphylococci from all surface wounds and hasten the time of grafting. The Lannette Wax cream proved more effective than the powder, which occasionally gave pain. It is usually unnecessary to administer systemic penicillin for locally infected burns unless there is evidence of uncontrolled spread of infection, metastatic infection or bacteremia.

WOUNDS. Penicillin has been tried in war wounds of all types. Most of the literature now available is concerned with local therapy; but a recent report by Florey and Cairns¹⁴ emphasizes the advantage of combined systemic and local therapy in severe wound infections, for, in any spreading cellulitis or invasive infection, the presence of a bacterial inhibitory substance in the blood stream is of greater value than is an agent applied topically to a wound containing varying amounts of slough. This was adequately demonstrated by Lyons²⁸ working at the Halloran General Hospital with infected war wounds. As in burns, the drug may be applied in an ointment, as wet dressings or in a powder. Pulvertaft³⁴ reports good results with the use of local penicillin in wounds. He feels that it is most important to explore and to drain any deep pockets of pus. He used penicillin in a powder, a spray and wet dressings. He too supports the view of Bodenham⁶ that, while the gram-positive organisms disappear rapidly, the gram-negative organisms may appear in even greater numbers. Jeffrey²⁴ corroborates the statements of Pulvertaft, and feels it is essential to maintain drainage. He did not think that the presence of gram-negative organisms significantly delayed healing.

In their report of their experience in North Africa, Florey and Cairns¹⁴ state that ointments and powders were not as successful as instilled solutions or wet dressings. Chronic sepsis of compound fractures responded to systemic therapy if loculated abscesses were not present. One hundred and seventy-one dirty wounds were treated locally with solutions of penicillin. Of them, 53 were sutured around rubber tubes, permitting local use of a solution containing 250 units of penicillin per cc. Complete healing occurred in 104 of the 171 cases, whereas 60 healed in part by granulation tissue, and 7 failed to heal. Healing took place even though the wounds contained *B. pyocyaneus*. The hospital stay was shortened by 3 to 6 weeks. In the prophylaxis and treatment of infection in compound fractures of long bones, those of the femur gave the poorest results. They felt that systemic treatment was inadequate in dosage and duration.

Brain wounds 3 days old or older were excised and sutured. A fine rubber tube was led through a stab hole into the cavity which was irrigated for 4 to 5 days with a solution containing 250 units per cc. The average amount used in each case was 15,000 units. Of 23 cases treated, 3 patients died. Wound healing was by first intention in 6 cases, while in 13 there was slight gaping of the wounds. Temporary sinus formation was common. Small osteomyelitic foci tended to prolong drainage of the wound. Thus it appears that in cases where the drug can be brought into adequate contact with the causative organism, whether saprophytic or tissue invaders, the results are beneficial.

Mary Florey and Williams¹⁶ recently reported in *The Lancet* a comparative study of 212 hand infections. About half of these were treated with local penicillin, and others treated by other means. Both groups received adequate surgical care. Penicillin-treated cases seemed to show an earlier regression of infection than the non-treated cases. Pus was

scanty or absent in the treated cases. Tissue destruction was stopped, pain relieved, and the number of dressings required were reduced in the treated cases. In comparison with the infections treated by the other means, the healing time of those treated with penicillin was considerably shorter. Bone lesions responded equally as well and healed with regeneration of bone. It was possible to start active motion of the penicillin-treated hands much earlier. Locally applied powdered calcium salt was somewhat painful. It was estimated that in 35 of the penicillin treated cases, a total saving of 1000 man days was accomplished as compared to a similar number of control cases.

Clostridial Infections. There is considerable controversy about the value of penicillin in the treatment of clostridial infections. It was recognized by the early investigators that penicillin *in vitro* was capable of inhibiting these organisms.^{2,7} Since these infections are so varied, it will be difficult to evaluate the place of any agent in a short period of time. This type of infection is frequently suspected and diagnosed, but errors in diagnosis are often made. The striking difference in morbidity and mortality between clostridial cellulitis and clostridial myositis was recently pointed out by MacLennan.²⁹ In experimental work with *Clostridium welchii* infections, penicillin is superior to the sulfonamides, as shown by Hac and Hubert.¹⁸ McKee, Hamre and Rake³⁰ demonstrated that tyrothricin was more effective than penicillin when applied locally to these organisms. It was the opinion of Lyons²⁸ that proteolytic clostridia recovered from war wounds required 4 to 5 times as much penicillin as do staphylococcal wound infections. The presence of these organisms indicates devitalized tissue or necrotic bone fragments.²⁸ Lyons highly recommends concentrated local therapy in conjunction with systemic treatment. Florey and Cairns¹⁴ treated 7 cases of gas gangrene, 3 of whom died. Jeffrey²⁴ was disappointed in the use of penicillin locally in gas gangrene. Cutler¹⁰ reported on 4 patients with major compound fractures who were treated with penicillin systemically and who developed gas gangrene which necessitated amputation. Recently Harvey and Meleney¹⁹ reported the treatment of 2 cases with penicillin, 1 infected with *Clostridium sordellii*, another with *Cl. welchii*, both of whom died. All of these investigators emphasize the necessity of giving sufficient specific antitoxin to patients with these infections, for penicillin will in no way alter the free circulating toxin. At best, it would only inhibit the organisms elaborating these substances. The treatment of anaerobic streptococcal infections has not been adequately investigated up to this time.

Chronic Infections. Penicillin should have great usefulness in the field of chronic surgical infections which include such diseases as bronchiectasis, multiple and single lung abscesses, chronic osteomyelitis and probably actinomycosis.

The treatment of chronic osteomyelitis with penicillin requires surgical removal of infected granulation and fibrous tissue, bone and sequestra in conjunction with systemic penicillin treatment, if improvement is to be more than temporary.⁸

Some strains of *Actinomycosis bovis* are inhibited *in vitro* by penicillin. Actinomycotic lesions may be arrested or completely cured with the use of penicillin in conjunction with surgical excision. The results are encouraging in the cases treated, but considerable time must pass before they can be classified as cured.

The use of penicillin in ulcerative colitis is of doubtful value, though a few patients have shown temporary improvement.^{25,41}

Prophylaxis. Penicillin may be useful in preventing postoperative infections. It may be useful in the prevention of infection in traumatic wounds, but adequate studies are not available at the present time. Florey and Cairns¹⁴ state: "There is little doubt that the prevention of infection with pyogenic cocci or its control in war wounds is within reach."

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OPHTHALMOLOGY

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TOXOPLASMIC CHORIORETINITIS

BY H. P. WAGENER, M.D.

THE rather recent discovery that the *Toxoplasma*, a genus of highly organized protozoan parasite, can invade the tissues of the eye and cause destructive lesions of the choroid and retina has introduced further com-

plexity into the etiologic study of chorioretinal disease. To most, if not to all, ophthalmologists the determination of the causative factor in any individual case of acute, subacute or inactive choroiditis has always been a difficult problem. To the earlier and more commonly recognized sources of ocular infection, syphilis, tuberculosis, the acute infectious diseases and blood stream infections, there have been added in the course of the years focal infections, sarcoidosis and brucellosis. And yet the true etiology of many cases remains obscure. In most instances in which the lesions were discovered during infancy and in many of those seen in early childhood, especially when the lesion was seen in the inactive stage, the rather vague diagnosis of congenital maldevelopment or intra-uterine inflammatory process has been made. The demonstration that certain of these lesions in infants are due to *Toxoplasma* infection, which, as Pinkerton and Henderson¹² suggest, must occur prenatally as the result of latent or subclinical infection in the mothers, makes it imperative that all of these infants be studied more carefully from the standpoint of the associated presence of intracerebral calcification and the possible presence in the blood of *Toxoplasma* antibodies. The implied fact that adult infection by *Toxoplasma* must occur suggests also the necessity of including tests for toxoplasmosis in the routine study of cases of chorioretinitis of obscure etiology.

According to Wolf and Cowen,^{20,21} Levaditi⁸ and his co-workers in 1928 were able to produce a severe inflammatory reaction in the eyes of rabbits by direct inoculation of emulsions of brain tissue infected with *Toxoplasma*. "There was intense iridocyclitis, destruction of the cornea, accumulation of exudate containing parasitized macrophages in the anterior and posterior chambers and perivascular infiltration about the papilla. Encysted *Toxoplasma* were found in retinal neurones. In some instances the central nervous system became secondarily infected, possibly by extension along the optic nerves." In a few rabbits extension of the infection along the optic nerves was observed after cerebral inoculation. No definite statement was made as to the involvement of the eye by this mode of extension.

According to Koch and his co-authors,⁶ Hepding⁴ in 1938 reported the occurrence in a cock of spontaneous toxoplasmic chorioretinitis resembling that later observed in man. Along with mild upper respiratory symptoms, chemosis of the left conjunctiva and cloudiness of the cornea developed. Histologically, the eye showed a widespread necrosis of the retina around the optic nerve with smaller foci of necrosis in the middle third of the retina. The peripheral part of the retina was infiltrated by large mononuclear cells. There were some swollen, large mononuclear cells and fibrin in the posterior part of the vitreous. The uveal tract was infiltrated by lymphocytes and plasma cells. The optic papilla was intensely infiltrated by round cells and fibroblasts. Single *Toxoplasma* and cystic forms were present in the lesions.

Probably the first case to be recorded in which *Toxoplasma* were demonstrated in the tissues of the human eye was that reported by Janku⁵ in 1923. A boy, 11 months old, was observed to have a small left eye when 3 days old. At about 3 months of age he was thought to be blind. He developed hydrocephalus and later convulsive seizures. In the macular region of each eye was an area of retinal and choroidal atrophy with marginal pigmentation. There was apparently secondary optic atrophy and some question of elevation or detachment of the nasal peripheral retina in the left, partially microphthalmic eye. The child died, probably at the age of 16 months. Quoting from Wolf and Cowen's summary:

"At autopsy an enormous internal hydrocephalus due to blocking of the aqueduct of Sylvius was present . . . The eyes showed chronic inflammatory and productive changes in the choroid and retina in the macular region producing the ophthalmoscopic picture of a coloboma. Sporocysts, which the author considered to be sporozoa, were found in the retinal lesion in the right eye. Huge vacuolated mononuclear cells in one part of the lesion in the left eye were thought to be of parasitic nature and related to the sporocysts in the other eye. This protozoan infection was considered to have been transmitted *via* the placenta into the arterial system of the choroid causing a chronic inflammatory process in the latter with secondary changes in the retina. A hyperplastic tumor-like formation of the left eye was felt to be due probably to the influence of the infection on the course of embryonic development." The parasite in this case, though probably *Toxoplasma*, was not so identified by the author.

A case, which was regarded by the authors as essentially identical with that of Janku and in which parasites were found which were later identified as *Toxoplasma*, was reported in 1937 by Wolf and Cowen¹⁹ under the title, "Granulomatous encephalomyelitis due to an encephalitozoan." A child, aged 24 days, had convulsive seizures and what appeared to be active areas of chorioretinitis in each eye, and a healed area of chorioretinitis in the right eye. The maculas were not involved apparently. The child died at 30 days of age. Histologically, the pathologic picture in the central nervous system "consisted of a widely disseminated encephalomyelitis in which the severest lesions were associated with necrosis and caseation primarily in the periventricular gray and white matter, and to a lesser degree in the cortex of the cerebrum. Miliary granulomas scattered throughout the central nervous system were a striking feature of the process. . . . A localized chorioretinitis was present in each eye, and here as in the brain, necrosis and caseation occurred in the affected areas." Judging from the detailed description of the histologic findings it would appear that the lesions, especially the evidences of edema and necrosis, were more marked in the retina than in the choroid and were especially severe in the inner layers of the retina. The parasites also were found in greater numbers in the retina than in the choroid.

In brief, histologically, foci showed centrally total necrosis of almost all the retinal elements, with marked swelling of the retina in places. Only cellular debris and scattered plasma cells and lymphocytes remained. The retinal pigment epithelium was disrupted with a dispersion of the pigment into the surrounding tissues. In the retina about the necrotic zones, the nerve fiber, ganglion cell and internal molecular layers were edematous and infiltrated by plasma cells, lymphocytes, occasional eosinophils and lipoid laden phagocytes. The ganglion cells were missing or degenerating. The deeper retinal layers showed edema with some infiltration by lymphocytes, neutrophils and monocytes. Some cellular exudate was present on the surface of the internal limiting membrane of the retina with some tendency to infiltrate into the vitreous. Edema and infiltration like that in the retina were present in the choroid, chiefly in the inner layers. There was hyperplasia of the endothelium of many of the vessels of the choriocapillaris. The pial and arachnoidal sheaths of the intra-orbital portion of the optic nerve were infiltrated by monocytes, lymphocytes and plasma cells and there was some extension into the substance of the nerve. Parasites were not found in these last lesions.

The first case observed clinically in which the parasites found microscopically in the lesions were proven definitely by animal inoculations to

be *Toxoplasma* was reported in 1939 by Wolf, Cowen and Paige.²¹ This was an infant taken ill at 3 days of age with convulsive seizures, disturbances in respiration and symptoms of spinal cord involvement. The infant died at the age of 31 days. "Terminally, irregular reddish brown areas were observed ophthalmoscopically in each macular region." The infant had a left Horner's syndrome, deviation of the eyes to the right, and nystagmus to the right. According to Koch and his co-authors, it was thought clinically that these macular lesions were hemorrhages resulting from cerebral birth trauma. At necropsy, however, there was found a widespread encephalomyelitis characterized by focal areas of inflammation and necrosis and by disseminated miliary granulomas. Histologically, the lesion in the right eye proved to be a localized chorioretinitis. A protozoan morphologically identical with *Toxoplasma* was present in all the lesions.

In 1941, Sabin,¹³ who, in 1937, in association with Olitsky, first demonstrated in a guinea pig the occurrence of *Toxoplasma* in North America, reported 2 cases of encephalitis in children in which the *Toxoplasma* were definitely established as the etiologic factor. The mode of infection was not established. He did not observe retinal or choroidal lesions in either of these cases. At that time Sabin seemed to think that the only accurate method of diagnosis was by inoculation of the spinal fluid or heparinized blood, or both into mice or guinea pigs by the intracerebral or intra-abdominal routes. He stated that, prior to his 2 cases, "There is therefore definite evidence of toxoplasmic infection in only 1 human being, an infant with 'congenital' encephalitis; that the 4 other cases of congenital encephalitis associated with morphologically similar parasites are also examples of the same infection can be considered only as probable."

Sabin stated that the *Toxoplasma* might perhaps be found in direct examinations of the spinal fluid "in rare cases in which the disease is especially destructive to the nervous system, as in infants during the first days or weeks of life." He also stated that neutralizing antibodies against *Toxoplasma* apparently develop in human serum and may disappear as early as 6 weeks after the onset and that the presence of such antibodies would be strong evidence of toxoplasmic infection, which their absence would not exclude. Apparently these neutralizing antibodies may persist in the blood serum for a much longer period of time than was originally supposed since the diagnosis of toxoplasmosis has been established presumably in more recent cases by the presence of these neutralizing antibodies long after the probable onset of the disease.

Also in 1941, Pinkerton and Henderson¹² reported 2 cases of adult toxoplasmosis proven by animal inoculation. These were instances of acute febrile exanthematic disease closely simulating Rocky Mountain spotted fever and endemic typhus and having some features in common with certain of the atypical pneumonias. No mention is made of involvement of the eyes. They suggested as possible diagnostic procedures to aid in the establishment of the diagnosis skin biopsies, neutralization tests, spinal fluid examinations, examination of blood smears, blood cultures, and examination of the sputum in cases with lung involvement. The authors suggest the tick as a possible vector of the disease.

In October, 1942, Sabin¹⁵ reported the results of toxoplasma neutralization tests performed on sera from 151 selected individuals. The sera of 59 of these were found to be positive. Of a group of 13 children ranging in age from 1 day to 15 years who exhibited "cerebral calcification and/or chorioretinitis in the macular region associated with hydrocephalus, micro-

cephalus and/or convulsions, psychomotor disturbance, etc.," 10 showed positive sera, and 8 of 10 mothers of this group had positive sera. On the other hand, of a group of 10 children ranging in age from 9 weeks to 5 years, who showed "hydrocephalus or microcephaly without cerebral calcification or chorioretinitis," none had a positive serum, and only 1 of 4 mothers of this group examined had a positive serum. And of a group of 9 children ranging in age from 1 day to 5 years who had "convulsions, psychomotor disturbances, etc., without cerebral calcification or chorioretinitis," only 1 had a positive serum. One of 2 mothers of this group had a positive serum. Of a group of 10 patients with "chorioretinitis of unknown etiology resembling that seen in congenital toxoplasmosis," 9 had positive sera. These patients ranged in age from 8 years to 59 years. Of the sub-group of 4 in which the disturbance of vision had been noted first at the age of 5 or 6 years, all 4 had positive sera, as did their mothers.

In November, 1942, Levin and Moore⁹ reported a case of fetal toxoplasmic encephalitis. A boy, aged $3\frac{1}{2}$ months, had convulsions, mental retardation, microcephaly and several areas of cerebral calcification. The ocular fundi were thought to be normal. However, 2 months later, "The fundi showed pallor of the nasal portions of both optic disks and several large areas of old chorioretinitis. These were located in the lower temporal portion of the right fundus and in the upper temporal and lower nasal portions of the left. They were all sharply outlined and showed yellowish white patches with accumulations of pigment, chiefly at their margins, but also within the atrophic areas. The vitreous was clear and there were no hemorrhages or areas of edema in the retina." The blood from both the patient and his mother gave positive complement fixation tests for Toxoplasma, but did not contain Toxoplasma neutralizing antibodies. Sabin, who performed these tests, was not willing to accept these tests as unequivocal evidence of toxoplasmic infection.

In January, 1943, Crothers¹ reported a group of 10 cases presumed to have toxoplasmic infection. Among this group were included 7 children with chorioretinitis, convulsions and cerebral calcification. All of these children and all but 1 of the mothers (and this one was not tested) had Toxoplasma neutralizing antibodies in their blood serum. The ages of all the cases were not noted; the ages given were $4\frac{3}{4}$, $10\frac{1}{2}$ and 12 years. No details of the chorioretinal lesions were described.

In January, 1943, Koch, Wolf, Cowen and Paige⁶ reported 6 cases of toxoplasmic encephalomyelitis with ocular lesions in which the diagnosis was made on the basis of the clinical findings and was confirmed by the identification of neutralizing antibodies to Toxoplasma in the serum of all the cases. They called attention to the syndrome characterized by chorioretinal lesions, symptoms and signs of widespread involvement of the central nervous system, convulsions, frequently internal hydrocephalus, and cerebral calcification visible in roentgenograms of the head. The ages of the patients in this series ranged from 31 days to 11 years. The chorioretinal lesions were active in 2 patients, aged 31 days and 4 years respectively. In the latter case, the lesions were largely healed but a lesion in the left eye still showed some signs of activity. The lesions in the infant of 31 days, which were actively progressive when first observed, seemed to have become quiescent after 5 months of observation. The lesions were apparently multiple in all except 2 eyes. The macular region was involved apparently in all but 1 of the 12 eyes described. Of the 12 optic disks described, 4 showed simple optic atrophy, 2 secondary optic atrophy, 3 pallor without atrophy, 2 papilledema, and only 1 was normal. All 6 of

the children had strabismus, in 5 convergent, in 1 divergent. Three had searching nystagmus. Three eyes in 2 cases were said to be "small" and 1 in another case was described as microphthalmic. Pupillary membrane remnants were observed in 3 eyes, posterior cortical cataract in 1, and posterior lenticonus in 1. Cerebral calcification was noted in the roentgenograms of the head in 5 of the patients.

Koch and his co-authors include in their discussion another case previously reported by Wolf, Cowen and Paige,²¹ in which there was progressive hydrocephalus and small areas of calcification in the brain. The child died at 9 weeks of age. Both eyes appeared to be smaller than normal in size and showed ophthalmoscopically a large, apparently vascularized "membranous mass" posterior to each lens. This was considered clinically to be either a detachment of the retina, a persistent tunica vasculosa lentis, or a glioma of the retina. Microscopically, the masses proved to be toxoplasmic chorioretinitis with masses of partially organized granulation tissue extending into the vitreous from the retina.

Histologically, all the lesions described by Koch and his co-authors were in the active stage. (All of these patients were infants, less than 3 months of age.) There were focal areas of edema and necrosis of the retina, involving in some places all, and in others some of the layers of the retina. The marginal zones of the necrotic areas showed perivascular and diffuse infiltration by lymphocytes, plasma cells, and occasional polymorphonuclear cells, eosinophils, and lipid laden phagocytes. There was some infiltration and vascular and connective tissue proliferation into the vitreous. The retinal pigment epithelium was disrupted and some pigment cells tended to migrate into the retina. The choroid was moderately infiltrated by cells similar to those in the retina in areas corresponding to the retinal lesions, and the sheaths of the optic nerves were similarly infiltrated. "Toxoplasmas were present in the retinal lesions and in general were most frequent where the lesions were most severe. Occasional parasites without accompanying reaction were observed in relatively normal portions of retina near the margins of inflammatory foci. They occurred singly or in clusters, free or intracellularly, or as 'cysts.' They were rare in the choroid."

With reference to the pathogenesis of the ocular lesions, Koch and his co-authors believe that the disease has its inception during fetal life, and that the parasite probably reaches the brain and other organs by way of the fetal circulation from the placenta. They think it possible but not likely that, after the brain has been infected, the infection passes by way of the subarachnoid space in the optic nerve sheaths to the interior of the globe. They think that the presence of the chorioretinitis during intra-uterine life may interfere with the normal development of the eye since microphthalmos and other congenital defects occur. But this interference must take place rather late in the period of gestation since no major malformations of the eye or nervous system have been found.

Koch thinks that the earliest phase of the chorioretinal lesion produced by the *Toxoplasma* is represented ophthalmoscopically by localized edema with indefinite peripheral demarcation and early necrosis in the central part of the lesion. The retinal vessels are normal. Later, the central part of the lesion becomes definitely atrophic so that the sclera becomes visible. Pigment clumps appear at the border of the central atrophic area and pigment in more granular distribution in and at the margin of the edematous peripheral zone. Still later the lesion loses the appearance of edema, becomes sharply margined, and may show atrophic and depressed zones,

or else elevated, avascular, homogeneous fibrous masses with possible invasion of granulation tissue into the vitreous. The entirely healed and inactive lesions appear as "sharply margined areas of chorioretinal atrophy or proliferation, of varying degree, with diffuse irregular pigment deposition, more concentrated at the margins. The retinal vasculature remained surprisingly normal."

Koch and his co-authors think that toxoplasmic chorioretinitis occurring in infants and young children must be differentiated from pseudoglioma, intra-ocular tumors, especially retinoblastoma, traumatic lesions (birth injuries), hereditary cerebromacular degeneration, congenital developmental defects, tuberosus sclerosis, acute metastatic chorioretinitis in upper respiratory infections, acute exanthems, malaria and the like, tuberculous or other forms of meningitis, and syphilitic, tuberculous and leprous granulomas. They present as characteristic features of toxoplasmic chorioretinitis: "(1) occurrence of severe and extensive focal chorioretinal lesions in infants and children; (2) regularity of bilateral involvement of the macular region; (3) tendency to bilateral occurrence of other lesions; (4) tendency to involvement of the periphery in one or more quadrants of the retina and choroid; (5) punched-out appearance of large and small lesions in the late phase; (6) occurrence of massive chorioretinal degeneration, extensive connective tissue proliferation and heavy pigmentation, as contrasted with the dissociation of these changes in other chorioretinal lesions; (7) presence of an essentially normal retina and vasculature surrounding the lesions in all stages of the infection; (8) tendency to the occurrence of associated congenital defects in the eyes; (9) rapid development of sequential optic nerve atrophy; and (10) constant clarity of the media in the presence of severe chorioretinitis (with one exception, the left eye in Case 4)." They think that the other clinical signs and symptoms present in the case are helpful in the diagnosis when the ophthalmoscopic findings are not clearly diagnostic. "Symptoms and signs beginning at birth or early in life, a subacute or chronic course, evidence of widespread involvement of the nervous system, convulsive seizures, internal hydrocephalus, and the occurrence of intracerebral calcification all point to the presence of infantile toxoplasmic encephalomyelitis, of which toxoplasmic chorioretinitis is an outstanding feature. Antitoxoplasmic activity of the serum tends to confirm this diagnosis." They state further: "It would appear that toxoplasmic chorioretinitis occurs in most, if not in all, instances of infantile toxoplasmic encephalomyelitis and is of diagnostic aid in the clinical recognition of this disease. It should be regularly sought in infants and children with a history of convulsions, hydrocephalus, mental retardation, speech difficulties, defective vision, or intracerebral calcification first observed in early infancy."

The occurrence of toxoplasmic chorioretinitis and encephalomyelitis in twin infants was reported by Heath³ at the recent meeting of the American Ophthalmological Society. The details of these cases are not available for presentation here, since they have not been published as yet. Heath seems to believe, along with Koch, that the chorioretinal lesions in these cases are always bilateral, are essentially always multiple, essentially always involve the maculas, and that they are most frequently associated with congenital anomalies of the eyes. It may be of interest that I have observed recently a single unilateral healed and atrophic chorioretinal lesion which did not involve the macula, in an infant with congenital hydrocephalus and multiple small areas of intracerebral calcification in the roentgenograms of the head. The blood serum of this infant possessed

neutralizing antibodies to *Toxoplasma*. The eyes appeared to be otherwise normal.

In 1943, Vail, Strong and Stephenson¹⁶ reported 6 patients with chorioretinitis in whom the lesions were apparently associated with *Toxoplasma* infection. Four of the patients were children, aged 7, 7, 7 and 12 years, at the time of the first discovery of the choroiditis. One patient was 16 years of age and the other 23. Neutralizing bodies against *Toxoplasma* were found in the blood sera of both the patient and the mother in all 4 of the children and the authors considered the disease to be of congenital origin in 1 other case also. They believed that, in the 6th case, it had been acquired in later life. In 3 of the cases the lesions were healed and inactive. In 3 the lesions were progressive though, at the time of the first examination, they appeared to be inactive. Three patients showed unilateral and 3 bilateral involvement. In 1 patient, at the first examination, a diagnosis was made of bilateral central chorioretinitis and bilateral secondary optic atrophy of congenital origin. The lesions in the maculas were apparently healed and showed no change during an observation period of 4 years. One year later the chorioretinitis had been disseminated throughout the left eye. Two years after this an acute anterior and posterior uveitis developed in the left eye, subsided in about 1 month, recurred 4 months later, and again subsided in about 6 weeks. At this time, the chorioretinitis was observed to be disseminated in each eye with recurrent active foci. In the 2 other patients in whom there was evidence of active inflammation, the lesions were unilateral; in 1 single and involving the macula, in the other multiple but not involving the macula. Of the 3 inactive lesions, 1 was unilateral and involved the macula; the other 2 were bilateral and disseminated with involvement of the macula. Evidence of cerebral calcification was found in only 1 of the cases. Two of the patients had convergent strabismus. No mention is made of any other congenital anomaly of the eyes.

In general summary of the eye lesions which they had observed, Vail, Strong and Stephenson¹⁶ state: "The fundus usually reveals a chorioretinitic lesion, unilateral or bilateral, having a predilection for the macular area. It has a grayish white center, is irregular, bordered with dark pigment, and surrounded on one or more sides by faint choroidal hemorrhage. The spread of the lesion is usually in the direction of the hemorrhage. The lesion may be elevated. Iridocyclitis, vitreous opacities, retinitis proliferans, and detachment of the retina may result. Central vision is always adversely affected." In this statement, the authors evidently have reference to some characteristics of the acute or active lesions which, in their opinion, may be of etiologic diagnostic significance. They state with reference to the inactive lesions that "nothing characteristic was found in the fundi that could classify them as typical of *Toxoplasma*." They believe that infection with *Toxoplasma* may be more prevalent among the general population than has been generally supposed and that in any obscure pathologic condition of the eye, tests for the presence of *Toxoplasma* neutralizing antibodies are indicated. They conclude that "many cases of chorioretinitis formerly diagnosed as tubercular, metastatic, or of unknown etiology may be due to *Toxoplasma*, especially if associated with cerebral calcification."

Also in 1943, Lichtstein and Solis-Cohen¹⁰ reported 2 cases of familial epilepsy under the diagnosis of familial tuberous sclerosis. The father, aged 46, had had 2 epileptic seizures during a 12-year period. Roentgenograms of the skull revealed 2 small calcifications in the region of the left

lateral ventricle. The eyegrounds were normal. The son, aged 22, had had epileptic attacks since the age of 2 and showed some evidences of mental deterioration. Roentgenograms of the skull showed a number of small, irregularly calcified deposits, probably within the ventricles. Vision was poor. Ophthalmoscopic examination revealed extensive choroidal changes with large areas of atrophy in the maculas and moderately advanced optic atrophy. The eyes were highly myopic. "The lesions were believed by the ophthalmologist to be on the basis of a hereditary macular degenerative process, congenital and colobomatous in origin." Merritt and Aring¹¹ and also Koch⁷ expressed the opinion that these were really cases of toxoplasmic encephalomyelitis. In his comment, Koch states: "Typical retinal tumors, not unlike the surface of an unripe mulberry in appearance, invariably occur in tuberous sclerosis, while in congenital or infantile toxoplasmic encephalomyelitis there are seen essentially without exception bilateral, more or less atrophic as well as pigmented, central (or macular) as well as more peripheral, fairly extensive patches of chorioretinitis. It is most probable that the onset of these patches in their acute phases occurs prenatally or in infancy or in both but not in childhood or later. There is no reason, however, to suppose that they do not continue to exist throughout the life of the afflicted patient or that they do not remain diagnostically recognizable. The latter is equally true with regard to the characteristic tumors of the optic disk and of the retina in tuberous sclerosis, an entity in which chorioretinitis has not yet been observed as such, probably for the very good reason that the tumors are not inflammatory or microörganistic in origin."

There would seem to be no better way to summarize the situation with regard to toxoplasmic chorioretinitis as it appears to stand today than by some quotations from a recent article by Vail. "Cases of disseminated and circumscribed exudative chorioretinitis are relatively common." "The etiology of chorioretinitis, however, presents many problems and in far too many cases the cause perforce remains obscure. It is for this reason that evidence which indicates that a parasite which is probably not rare produces choroiditis in some cases assumes importance and warrants discussion, even if the evidence may not be quite complete." "The ophthalmologic findings in both the infantile and adult cases are the familiar ones of circumscribed exudative choroiditis. There is a predilection for the macular area and the lesions are usually bilateral and multiple." "In 11 of the cases described the condition was probably congenital, in the 12th it was without doubt acquired. Three additional cases occurring in adults past the third decade under my observation have not yet been reported. These are probably acquired cases of toxoplasma." Vail points out that, although Koch and his associates think that there are some ophthalmoscopic diagnostic features of toxoplasmic chorioretinitis, he has not been able to make the diagnosis from the ophthalmoscopic appearance alone in the older children and adults he has seen. The diagnosis depended on the demonstration of *Toxoplasma* neutralizing antibodies in the blood serum. Vail¹⁷ thinks that more studies are needed to prove the validity of this neutralization test. The test as at present performed seems to be of considerable difficulty. Perhaps more cases would be discovered if a more universally applicable and, at the same time, reliable laboratory test was devised. Sabin¹⁴ spoke in 1941 of the possibility of a complement-fixation test of which Warren¹⁸ and he stated in 1942, "While a positive complement-fixation reaction does not in all cases indicate active or even recent infection, it is believed that this test may

have its greatest usefulness in the rapid diagnosis of active toxoplasmosis." There seems to be no very satisfactory treatment for this disease, though various forms of sulfonamides have been tried.

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BOOK REVIEWS AND NOTICES

AMERICAN MEN OF SCIENCE. A Biographical Directory. Edited by JACQUES CATTELL. Seventh ed. Pp. 2003. Lancaster, Pa.: The Science Press, 1944. Price, \$14.00.

THIS well-known and invaluable book of reference requires no explanation or recommendation to American scientists. We agree with the Editor that the advantage of having an enlarged revised edition at this time outweighs the disadvantages associated with war-time production; and that, if only from the point of view of saving scientists' time and energy, it is a contribution to the war effort. The new edition contains about 34,000 names, as compared with 4000 in the first edition, and 28,000 in the sixth. "A selection has again been made by their colleagues of the 250 total additional selections for this edition(?) who in the course of 5 years have attained a position among our leading scientific workers . . . by the same methods as those used in previous editions." This presumably refers to the asterisks appearing before the name of each individual's specialty. In the case of certain individuals, the small number following the asterisk indicates the edition in which it first appears. Possible modifications of this procedure were not put into effect, as the A. A. S. Committee appointed to study the subject has been prevented from functioning by the war.

We recommend the volume highly to all those engaged in scientific work.
E. K.

SYNOPSIS OF OBSTETRICS. By JENNINGS C. LITZENBERG, B.Sc., M.D., F.A.C.S., Professor Emeritus of Obstetrics and Gynecology, Univ. of Minnesota Medical School, Minneapolis. Second ed. Pp. 405; 157 illus. (5 in color). St. Louis: C. V. Mosby, 1943. Price, \$5.00.

THIS book gives a very concise and complete review of obstetrics. It is well written, very clear, and contains many valuable illustrations. It makes an excellent teaching manual. I recommend it highly for a quick review of obstetrics.
H. F.

CIVILIZATION AND DISEASE. By HENRY E. SIGERIST, M.D., D.LITT., LL.D., William H. Welch Professor of the History of Medicine in Johns Hopkins University. Pp. 255; 52 figs. Ithaca, N. Y.: Cornell Univ. Press, 1943. Price, \$3.75.

THE 12 chapters of this latest production of a prolific pen are expanded from the 6 Messenger Lectures given at Cornell by Dr. Sigerist in 1940. They consider the relationships between disease and such facets of civilization as economics, the law, social life, history, religion, philosophy, science, literature, art, music. The opening and longest chapter, Civilization as a Factor in the Genesis of Disease, discusses the rôles of nutrition, of costume and personal hygiene, of housing and sanitation in the production of disease. This is well-balanced by a final chapter on civilization's progress in the struggle against disease.

The treatment of the subject matter is from the historical point of view, aimed at the layman, and necessarily fragmentary, presumably because of space considerations. However, the Author quickens our interest by the insertion of many critical and illuminating comments, which rise in powerful crescendo through the last few pages. It may be a cliché to say that in this country the technology of medicine has out-run its sociology—but this detracts

not at all from the value of Sigerist's emphasis on the need for cutting down the number of unnecessary and premature deaths and lost working days. Furthermore, no one can properly object to the position he takes that poverty, ignorance and medical ineffectiveness are the chief factors in lowering health conditions. Dr. Sigerist's years of careful study of Soviet medicine and health maintenance, which have made him easily the best informed authority on this subject in the United States, have led him to what many authorities regard as too radical a stand on these matters as applied to America. But this aspect he leaves largely untouched in this book; and surely we may all agree with him that standards of living and of education and health conditions must be raised as high as possible throughout the world. True is it also that "a new medicine serving a new society requires new forms of service." But what is a reasonable interpretation of "as high as possible" and what should these new forms of service be? There's the rub! The Reviewer humbly acknowledges that he neither practices medicine nor concerns himself closely with the very necessary activities of organized medicine. Even so, however, it seems almost inevitable that the American temperament, and our economical and educational standards and medical efficiency being what they are, the introduction of sweeping and revolutionary governmental control and centralization of power in the hands of a single federal official would shortly replace our sound evolutionary progress toward new forms of medical service (slow though it may be), with a degradation of medical efficiency that would far outweigh any advantages gained.

E. K.

THE MEDICAL CLINICS OF NORTH AMERICA. Chicago Number. Symposium on Cardiovascular Diseases. Pp. 289; 37 figs.; 7 tables. Philadelphia: Saunders. Price, \$16.00 per year.

THE January 1944 number of the Medical Clinics of North America contains 2 interesting symposia. The first deals concisely, yet adequately, with several broad problems of cardiovascular diseases in the usual direct manner of the "Clinics." Diseases of the blood-forming organs constitute the theme of the second symposium, with emphasis placed on the increasingly important subject of the Rh factor in 2 of the 7 articles of this group.

An isolated article on the treatment of Pneumonia with Sulfadiazine, and another reemphasizing the ever-present errors in diagnosis of neoplastic lesions of the large bowel conclude this number from Chicago.

R. M.

PANCREATIC FUNCTION AND PANCREATIC DISEASE STUDIED BY MEANS OF SECRETIN. By HENRIK O. LAGERLOF, M.D. Translated by HELEN D. DREY. Foreword by JOSEPH H. PRATT, M.D. Pp. 289; 50 tables. Printed in Sweden. New York: Macmillan, 1942. Price, \$3.50.

THIS book deals primarily with the technique, results and interpretation of the secretin test for pancreatic function. At the same time the physiology and the clinical disturbances of the pancreas are presented under these chapter headings: normal external pancreatic secretion, acute pancreatic disease and chronic pancreatitis, the secretin test, general discussion and case reports.

The procedures for the determination of the bicarbonate, amylase, trypsin and lipase content of pancreatic juice are amply and clearly outlined. Factors that may influence results are also emphasized. For practical purposes, the book stresses the value of the bicarbonate and amylase determinations alone as sufficing to indicate the functional or pathologic state of the pancreas.

One strong feature of the text is the emphasis on the statistical treatment of the figures obtained. Thus, one gets the impression that the final figures and the conclusion derived therefrom are much more reliable than are the customary average medical quantitative reports.

Some space is devoted to the clinical aspects of pancreatic disease. The case reports, with their operative or autopsy findings, attempt to correlate the laboratory tests with the strictly clinical picture.

By way of recommendation, one may state that the physiologic action of the Swedish preparation of secretin (which is the basis of the studies in the book) and its diagnostic value have been demonstrated and confirmed in this country by such students of pancreatic function and disease as Diamond, Comfort and Pratt.

The book will be useful to the gastro-enterologist and to any physician interested in hepato-biliary-pancreatic disorders. G. A.

TEXTBOOK OF GYNECOLOGY. By EMIL NOVAK, M.D., F.A.C.S., Associate in Gynecology, The Johns Hopkins Medical School; Gynecologist, Bon Secours and St. Agnes Hospitals, Baltimore. Second ed. Pp. 708; 456 figs. Baltimore: Williams & Wilkins, 1944. Price, \$8.00.

THE first edition of Novak's text appeared in 1941 under the title *Gynecology and Female Endocrinology*. The present volume has been expanded by nearly 100 pages. A chapter has been contributed on the common disorders of the female urinary organs by Houston S. Everett. The volume is written primarily for the student and general practitioner. One of its chief values lies in the large number of beautiful illustrations, many of which are produced in color. Its chapters on female endocrinology give the reader an excellent review of the problems which sometimes are brought to the gynecologist who is interested in this branch of his subject. This volume is to be highly recommended as a classroom text. D. M.

RECENT ADVANCES IN MEDICINE. By G. E. BEAUMONT, M.A., D.M. (OXON.), F.R.C.P., D.P.H. (LOND.); Physician to the Middlesex Hospital, Hospital for Consumption and Diseases of the Chest, Brompton; Lecturer in Medicine, Middlesex Hospital Medical School; and E. C. DODDS, M.V.O., D.Sc., PH.D., M.D., F.R.C.P., F.I.C., F.R.S. (EDIN.), F.R.S., Courtauld Professor of Biochemistry in the University of London (Middlesex Hospital). Eleventh ed. Pp. 412; 43 figs.; many tables. Philadelphia: Blakiston, 1943. Price, \$5.50.

THE 11th edition of this small handbook suggests that it fills a definite need for both practicing physician and student alike. The book reflects the British point of view and differs in some respects from the American teachings. For example, the evaluation of the sulfonamide drugs now in use does not seem to be supported by the American literature on this subject. The discussion of electrocardiography fails to emphasize significantly the importance of chest leads; and, in fact, the authors still speak of only one chest lead.

Although there are points of value in this monograph it seems to the reviewer that better material is available elsewhere. F. M.

OLD AGE IN NEW YORK CITY. An Analysis of Some Problems of the Aged, Based on 3106 Requests for Information About Health and Welfare Services. By HELEN HARDY BRUNOT. Pp. 128; many tables. New York: Welfare Council of New York City, 1944. Price, \$1.50.

A USEFUL and highly commendatory attempt to solve some of the problems of aging, which have aroused much interest during the last few years, has been the creation of a Bureau for the Aged by the Welfare Council of New York City. This group has now brought out a study of old age in that city. Under the direction of this Bureau, the important factors that make up the problem of aged people have been classified and critically examined.

The inquiry upon which this report is based is extended over a 2½ year period, during which 3106 requests for information were received. These requests were carefully investigated and evaluated in order to show the type of personal problems that were being faced by the old people of New York

and their experiences with the available community agencies to which they turned for assistance.

The body of the report is divided into 5 sections. After dealing with the function of the Bureau, the sources of material and the methods of investigation, sections follow which take up the age and sex distribution of the group studied and their social and economic backgrounds, the problems of physical and mental health in old age, the question of support in old age, and, finally, social relationships and environment as applied to the aged.

One result of this study has been to confirm the dictum, "That old age itself does not constitute a social problem since it is natural and inevitable but that the conditions which surround the aged, including the attitude of younger people, create the problem." The report is a well-prepared, clearly stated and thoughtful document. It is based upon a painstaking, scientifically conducted investigation in which the investigators approached their problems not only intelligently but with a sympathetic understanding. The report can be studied with profit by all agencies and all individuals who are concerned with the welfare of older people. Until social agencies, the general public, and particularly families and friends of older people, are firmly impressed with the fact that, "the first requisite to a more intelligent and humane community program for services aimed to benefit aged persons is a recognition of their individuality as persons," no program can serve effectively the needs of the ever-increasing number of older individuals, not only in New York City but in all of our communities.

G. P.

THE JEWS AND MEDICINE ESSAYS. By HARRY FRIEDENWALD, M.D., D.H.L. (HON.), D.Sc. (HON.), Professor Emeritus of Ophthalmology, University of Maryland. Preface by HENRY E. SIGERIST. Publications of the Institute of the History of Medicine, The Johns Hopkins University. First Series: Monographs. Volumes 2 and 3. Pp. 817; many figs. Baltimore: The Johns Hopkins Press, 1944. Price, \$3.75 per volume.

BUT a brief perusal of these essays is required to demonstrate the author's protracted and productive interest in Jewish culture and in the contributions of Jewish physicians to the progress of medicine. These volumes, which constitute the 2nd and 3rd volumes of the Monograph Series of Publications of the Institute of the History of Medicine, are composed of 42 articles mostly reprinted from, or in a few cases based on, previously published articles. They range over many years, from 1917 to the 1940s, and over a wide field—Jewish booklovers, practitioners and the practice of medicine, Jews and the Universities, hospitals, diseases of the Jews, and so on. Two monographs of more ambitious scope, listed as Chronicles, are on Jewish Physicians in Italy: Their Relation to the Papal and Italian States (63 pp.) and History of the Jewish Physicians of Spain, Portugal and Southeastern France (160 pp.). Though, for the most part, such Chronicles are drier reading than the warmer, biographic sketches, topical essays, and *obiter dicta*, they too have their proper place in a medical historical library, as valuable works of references.

The medical profession owes much to the Friedenwalds of Baltimore and not the smallest of our debt is that brought about by the publication of these 2 interesting and scholarly volumes.

E. K.

THE PRINCIPLES AND PRACTICE OF MEDICINE. Originally written by SIR WILLIAM OSLER, BART., M.D., F.R.C.P., F.R.S. Designed for the use of practitioners and students of medicine by HENRY A. CHRISTIAN, A.M., M.D., LL.D. (HON.), Sc.D., (HON.) F.R.C.P. (CANAD.), F.A.C.P. Fifteenth ed. Pp. 1498. New York: D. Appleton-Century, 1944. Price, \$9.50.

A NEW edition of "Osler" is always something to look forward to; it is especially satisfying to see this hardy perennial continuing to appear at such

frequent intervals—this being the 6th edition to be published in the past decade. It is also notable, in these days of multiple authorship, that a single author can keep a work of this size and scope so well abreast of the rapidly changing times.

As Dr. Christian, in his Preface, expresses pleasure in his contact with those voicing suggestions, and regrets that anonymous reviews prevent his pursuing the Reviewer's remarks farther (though doubtless the Editor would supply the Reviewer's name and address on request), the present Reviewer started notes as to suggested changes and modifications. As these, in print, however, could not avoid creating an erroneous atmosphere of adverse criticism where none was intended, and doubtless at times would contain no germ of improvement, the suggestions have been confined to private correspondence. For the book as a whole, there can only be praise.

Conforming to the policy started in the 14th (semi-centennial) edition, this edition has been "... so organized that important new material will be quickly incorporated, so that there will be in the future not occasional but frequent new editions of the text," and medical progress with its accelerated tempo thereby better presented. The slight handicap of rare blank or partly filled pages, with accessory numbering of pages (such as "72(1)"), is a small price for a reader to pay for the greater advantage mentioned. In fact, this may easily prove to be at least a partial answer to the loose leaf system as applied to medicine, with its tedious requirements of frequent shifting of old and new leaves.

As before, the text begins with functional nervous diseases and ends with organic nervous diseases, an unusual schism of doubtful advantage. Infections and parasitic diseases, intoxications and so on occupy almost half the book, the rest being taken up by diseases of the digestive and other systems. Due regard has been paid to the special needs raised by war conditions: the many tropical and venereal diseases, the increased chances of occurrence of various epidemics, the rise of new and potent drugs, the increased need for the newest and best methods of diagnosis, prophylaxis and treatment—"all of this will be found in this edition in a very complete and up to date fashion" (Preface). The dates of the articles included in the references at the end of each section amply confirm the up-to-datedness of this excellent book.

E. K.

OFFICE TREATMENT OF THE NOSE, THROAT AND EAR. By A. R. HOLLANDER, Associate Professor of Otolaryngology, Univ. of Illinois. Pp. 480; well illustrated. Chicago: Year Book Publishers, 1943. Price, \$5.00.

This book should be in the hands of all who treat conditions of the upper respiratory tract. All modern concepts of treatment are prescribed. The bibliography is excellent. The Reviewer gives unreserved recommendations.

K. H.

EVOLUCION Y FUNCION BIOLOGICA DE LAS PROTEINAS. By JULIO MENDEZ, Physician of the J. M. Ramos Mejia Hospital; Honorary Professor of the School of Medicine of Buenos Aires, Cordoba, and La Plata. Pp. 139. Buenos Aires: Guillermo Kraft, 1943.

This book consists of 6 lectures given by the author at the School of Medicine of the Universidad Nacional of Buenos Aires on the evolution and biologic functions of the proteins. The exposition is very clear and the style is eloquent and precise. He discusses the chemical structure of proteins and subdivides them into macroproteins (fibrinogen, fibrin, collagen), mesoproteins (euglobulins, pseudoglobulins), and microproteins (serum albumins, amino acids). It is a debatable question whether or not this classification tends to clarify the study of this group of compounds.

The name "lysins Mendez" is given to the amino acids in the body, and the rôle of these compounds as active agents in pathologic conditions is presented

as a theory of the author. Furthermore, some of the expressed concepts of allergy, anaphylaxis and immunity do not agree with the prevalent ideas. Water balance, edema, nephrosis, acidosis, alkalosis, inflammation, and so forth, are discussed.

The book provides interesting information regarding the author's point of view on some physiologic processes, though they may not be entirely in agreement with the current theories on the subject.

L. G.

A MANUAL OF MEDICAL PARASITOLOGY. By CLAY G. HUFF, Professor of Parasitology, Univ. of Chicago. Pp. 88; 10 plates. Chicago: Univ. of Chicago Press, 1943. Price, \$1.50.

PARASITOLOGISTS have complained for some time that their subject has not received adequate recognition in the curricula of medical schools in this country. Now that current circumstances have emphasized the importance of parasitic diseases and more time is being allotted to their study, one may wonder that there has been this neglect. Perhaps it has reflected the isolationist attitude of the nation, perhaps it has been a result of overcrowded curricula, or possibly it was related to the manner in which the subject had been presented.

This manual is an outgrowth of notes used for the past several years in the course in Medical Parasitology at the Univ. of Chicago. General arrangement of the text is shown by the following chapter headings: 1. Trematodes or Flukes; 2. Cestodes or Tapeworms; 3. Nematodes or Roundworms; 4. Intestinal Protozoa; 5. Hemoflagellates; 6. Malarial Parasites of Man; 7. Mosquitoes Which Transmit Disease; 8. Flies Which Transmit or Cause Disease; 9. Other Bloodsucking Insects Which Transmit Disease; 10. Ticks and Mites—Order Acarina; 11. Laboratory Diagnosis of Parasitic Infections.

The book is illustrated by 1 composite chart of trematode life histories (which is too complex for teaching purposes) and by several other simpler and more useful figures. The colored plate of 3 species of *Plasmodium* of man is especially good. In part the text is a conventional discussion, interspersed here and there with more or less extensive and detailed directions for laboratory exercises to which questions are appended.

This arrangement of the material brings the student into contact with uncommon parasites first, and laboratory exercises suggest study of details of morphology of parasites of man or of organisms from other hosts, which, while important to a student of parasitology as such, have no part in an understanding of parasitic disease, their diagnosis and control. Instruction in Parasitology in medical schools would accomplish its rightful aims if the students understood how animal parasites cause disease and how infections may be recognized and controlled. There is certainly not time for more extended considerations. When parasitologists come to understand that and present the subject accordingly, perhaps it will receive the attention it deserves. Professor Huff's manual is not a means to this end.

H. R.

MAURICE ARTHUS' PHILOSOPHY OF SCIENTIFIC INVESTIGATION. Preface to *De l'Anaphylaxie à l'Immunité*, Paris, 1921. Translated from the French, with an Introduction by HENRY E. SIGERIST. Foreword by WARFIELD T. LONGCOPE. (Reprinted from Bulletin of the History of Medicine, Volume XIV, No. 3, October, 1943, pp. 366-390.) Pp. 26. Baltimore: Johns Hopkins Press, 1943. Price, \$.75.

THE distinguished French physiologist, for whom the "Arthus phenomenon" is named, wrote a chapter of advice for those beginning a career of experimental physiology. In this preface he warns students against the "theoreticians" and extols the scientific method. The experimentalist is urged to seek the answer to only one question at a time, having formed the question in such a way that it may be answered by yes or no.

Dr. Sigerist has furnished an admirable translation.

M. M.

MANOMETRIC METHODS as Applied to the Measurement of Cell Respiration and Other Processes. By MALCOLM DIXON, Ph.D., Sc.D., F.R.S., Univ. Lecturer in Biochemistry in the Univ. of Cambridge. Foreword by SIR F. G. HOPKINS, O.M., F.R.S. Second ed. Pp. 155; 20 figs.; 6 tables. Cambridge: Univ. Press; New York: Macmillan. Price, \$1.75.

THE study of the metabolism of isolated surviving tissues *in vitro* has extended into many biologic and medical fields. Since the original development by Warburg, manometric methods for the determination of the gas exchange of such tissue have increased in number, complexity and refinement. Dixon's able book has always been a standard in this field and a new edition is welcomed by technologists in the field. The text has been thoroughly revised, and new sections have been added, *viz.*, measurements in serum, micro methods, and so forth. The bibliography has also been brought up to date. W. S.

MEDICINE AND THE WAR. Edited by WILLIAM H. TALIAFERRO. Foreword by WILLIAM T. HUTCHINSON, Executive Secretary, Charles R. Walgreen Foundation for the Study of American Institutions. Pp. 193; several figs. and tables. Chicago: Univ. of Chicago Press. Price, \$2.00.

WAR always reemphasizes human problems; economic, social, political, philosophic, ethical. Medicine also presents many aspects which in peace time are hazy and ill-defined, but which now require sharper delineation. This small volume contains a series of lectures given under the auspices of the Walgreen Foundation by a group from the University of Chicago Medical Faculty. It sums up in brief, clear and entertaining style most of the current war problems of medicine. The chapters which are particularly informative are those devoted to Chemotherapy; Malaria; Insects, Disease and Modern Transportation; and Shock and Blood Substitutes. Among other topics of general interest are: Food and the War; Aviation Medicine; Neurological and Psychological Effects of Cerebral Injuries; Psychiatry and the War; and Chemical Warfare.

The book is recommended reading to those who wish to obtain quickly a speaking acquaintance with recent progress and trends in these various aspects of war medicine. W. S.

MEDICAL CARE OF THE DISCHARGED HOSPITAL PATIENT. By FRODE JENSEN, M.D., Instructor in Medicine, Syracuse Univ. College of Medicine; H. G. WEISKOTTEN, M.D., Dean and Professor of Pathology, Syracuse Univ. College of Medicine; and MARGARET A. THOMAS, M.A. (OXON.). Pp. 94; 4 tables. New York: The Commonwealth Fund, 1944. Price, \$1.00.

THE University Hospital of Syracuse, N. Y., through its activity in teaching domiciliary medicine to medical students, became increasingly aware of the unsatisfactory nature of medical care for most of its ward patients after discharge from the Hospital. This book is a report of their experiment in extending medical supervision beyond the limits of the Hospital walls. Figures are presented showing that the extension of medical care shortened hospital stay and prevented readmission.

An instructor in Medicine was appointed as Extra Mural Resident, and he was assisted by a lay Social Investigator. All patients (902) discharged from the medical wards for a period of 18 months came within the scope of the project. The Extra Mural Resident discussed with them all their plans for care after discharge. He acted as family physician for the patients needing home care and having no private physician, and as a coordinator of medical care for those who could be served by the Dispensary; those who returned to the care of private physicians; and those who were discharged to institutional care. Since 84% of the total group were chronically ill, the emphasis of the report is on medical and social problems of this group.

If hospitals are going to become more concerned in preventive medicine and in patients beyond the acute stage of illness, this report is interesting as an indication of one method of approach to the problem. The method reported may not be the solution, or might require considerable modification to be practical, but it certainly is aimed at the solution of one of medicine's most besetting problems, *i. e.*, how to prevent waste of medical care. Anyone interested in this subject will find the bibliography of great value. M. P.

SAFE CONVOY. *The Expectant Mother's Handbook.* By WILLIAM J. CARRINGTON, M.D., A.B., F.A.C.S., Attending Gynecologist, Atlantic City Hospital, Atlantic County Hospital for Nervous and Mental Diseases, Pine Rest Hospital, Atlantic City Municipal Hospital and Atlantic Shores Hospital; Diplomate American Board of Obstetrics and Gynecology; Former Vice-President, American Medical Association. Pp. 253. Philadelphia, New York: J. B. Lippincott Company, 1944. Price, \$2.50.

THIS volume of 256 pages is a comprehensive consideration of the reproductive process which has been written for the expectant mother. The author writes in an entertaining manner and covers his subject well. He has deemed it necessary to include a glossary of some 350 terms. This fact leads the Reviewer to wonder whether the average expectant mother will be able to digest its contents with ease. With that one exception the volume is without adverse criticism. D. M.

THE CARE AND FEEDING OF CHILDREN. Revised and Enlarged by L. EMMETT HOLT, JR., M.D., Associate Professor of Pediatrics, Johns Hopkins Univ.; Associate Pediatrician, Johns Hopkins Hospital, Baltimore, Md. Sixteenth ed. Pp. 321; illustrated. New York and London: D. Appleton-Century, 1943. Price, \$2.00.

THIS latest revision of one of the oldest and most popular baby-raising guides contains new material on "simplified milk formulas, up-to-date food and vitamin data, information on allergy and inoculations, and a section on behavior problems, to mention a few" (quotation from the jacket). Its contents are organized under the following chief headings: Care of Infants, Growth and Development of Infants, Breast Feeding, Artificial Feeding, Feeble and Premature Infants, Older Children, Behavior Problems, and Common Ailments of Childhood. The discussions, arranged in short question-and-answer form, are couched usually in broad terms.

The curious mother of a baby or growing child will find in this book satisfying information regarding the common problems which come up while rearing a young citizen from cradle to adolescence. Though not every pediatrician would agree with every statement made, the textual advice conforms in general with the point of view of contemporary pediatric practice. I. W.

LABORATORY METHODS OF THE UNITED STATES ARMY. Edited by JAMES STEVENS SIMMONS, B.S., M.D., Ph.D., D.P.H., Sc.D.(Hon.); and CLEON J. GENTZKOW, M.D., Ph.D. Fifth ed. Pp. 823; 108 tables; 103 figs. (8 color plates). Philadelphia: Lea & Febiger, 1944. Price, \$7.50.

THIS edition, like the first, prepared to meet the current war time needs, is now, as one might readily imagine, considerably larger than its predecessor. Yet by the military conciseness of presentation that it possesses, a wide range of subject matter is kept within the limits of an easily manageable volume—no mean advantage for the many "huts" and "tents" to which this book will penetrate. Its 11 parts, none without great practical value, cover a considerably wider range than the usual work of laboratory diagnosis: Clinical Pathology, Chemistry, Mycology, Bacteriology, Rickettsiae and Filtrable Viruses, Protozoology, Helminthology, Medical Entomology, Pathology, Special Veterinary Methods, Statistical Methods of the more important sections.

Part I, so-called "Clinical Pathology," though including Pregnancy Tests, Blood Groups and Transfusions, and the Serodiagnosis of Syphilis, is considerably shorter (126 pages) than Part II on Chemistry (220 pages) and Part IV on Bacteriology (178 pages). The last Part, on Statistical Methods, by General P. R. Hawley, Chief Surgeon in the European Field of Operations, is a novel and desirable feature in a book of this kind. One approaches it hopefully as "designed for the laboratory worker, interested in fields other than mathematics." This tactfully expressed aim, however, has not produced a handy statement for the beginning user of statistical methods. The very condensed style in itself, makes it as difficult, or perhaps even more difficult, to follow than larger treatments of the subject.

Of the 25 contributors about one-half are from civilian life, and a good third are notable authorities. One may indeed wonder how such an excellent up-to-date job has been accomplished by men all of whom must be carrying heavy loads of routine. They have produced a first class handbook with the needs of the military kept to the fore, but one that is just as useful in civilian laboratories and to veterinarians and public health workers. E. K.

A MANUAL OF PHYSICAL THERAPY. Formerly published under the title "Physical Therapy for Nurses." By RICHARD KOVACS, M.D., Professor of Physical Therapy, New York Polyclinic Medical School and Hospital; Attending Physical Therapist, Manhattan State, Harlem Valley State, Columbus, and West Side Hospitals New York. Third ed. Pp. 309; 29 tables; 118 figs. Philadelphia: Lea & Febiger, 1944. Price, \$3.25.

In this revised edition the author has presented a brief, concise compendium of physical therapy, especially as it applies to the increasingly important rôle it is now assuming in the treatment of war injuries. The introduction gives the reader a picture of the scope, basis and history of physical therapy. Then the author presents an excellent discussion of the physics, physiologic effects, and the therapeutic application of heat, artificial fever, natural and artificial ultraviolet radiation, electrotherapy (including low frequency currents, long and short wave diathermy, static electricity, and electrodiagnosis), hydrotherapy, massage and exercise. There is included in the book a chapter by Dr. Madge C. L. McGuinness, who gives a comprehensive development of the physiology, classification and description of general and special exercises as they apply in the general practice of physical therapy; and as developed in the Army Reconditioning Program. There also is a chapter with suggestions and diagrams covering all the important points in the organization and conduct of a physical therapy department for institutional practice. The book is compact, clear, and concise, with an excellent organization of the subject by chapters. There are also review questions at the end of Parts 2, 3, 4 and 5 that add to the teaching value of the book.

It is the opinion of the Reviewer that the author has given to the field of physical therapy a brief, practical reference that will be a valuable addition to any library. W. T.

SMALL COMMUNITY HOSPITALS. By HENRY J. SOUTHMAYD, Director, Division of Rural Hospitals, The Commonwealth Fund; and GEDDES SMITH, Associate, The Commonwealth Fund. Foreword by BARRY C. SMITH, General Director, The Commonwealth Fund. Pp. 182. New York: The Commonwealth Fund, 1944. Price, \$2.00.

This book brings to the public the accumulated experiences of the Commonwealth Fund in their program to improve the quality of medical care in the smaller communities of this country. It should become the handbook of any group of citizens interested in this fundamental and vital problem. While written primarily for the layman, its detailed discussion of plans, organization, and procedures will be of inestimable value to physicians and administrators interested in the improvement of hospital and medical care in rural communities. R. B.

ORAL HISTOLOGY AND EMBRYOLOGY. Edited by BALINT ORBAN, M.D., D.D.S. Pp. 342; 262 illus., 4 color plates. St. Louis: C. V. Mosby, 1944.

THE rapid advance in knowledge of the oral tissues over the last decade has materially changed our histologic insight. Thereby also new light is spread on pathologic processes. Investigators in the histologic field often disagree as to findings and interpretations. This difficulty is overcome by proper planning of the book. Prominent men in the field of oral histology were requested to write outlines on different detail which they had personally investigated. The outlines were subsequently discussed and criticized by these men collectively. The different viewpoints were coordinated by the editor, embodied in chapters which were often redrafted and finally approved in essential by all contributors. Likewise the resources of all collaborators were pooled and the best illustrations of their material selected.

The student of oral histology is finally given a textbook in which confusion resulting from differences in opinion is avoided. Clinical applications are added to each chapter. The result is a textbook which is a real contribution to the practice of dentistry. We believe that the arrangement of the chapters could be improved upon. Thus Chapter I on the Development of the Face and Oral Cavity could have been followed by Chapter VIII Concerning the Maxilla and Mandible, Chapter XV on The Maxillary Sinuses, Chapter XIV on The Temporomandibular Joint, Chapter XII on Oral Mucous Membrane and Chapter XIII on Glands of the Oral Cavity. Chapter II dealing with the Development and Growth of Teeth is properly followed by Chapters III to VII on Enamel, Dentin, Pulp, Cementum and Periodontal Membrane, after which could have followed Chapters IX to XI on the Gingival Sulcus and Epithelial Attachment, Eruption of the Tooth and Shedding of the Deciduous Teeth. A closing Chapter XVI on Histologic Technic is appended. The marginal indices are helpful in reviewing the contents of the chapters. A concise review of the newer concept of amelogenesis is clearly expounded. The photomicrography is excellent and the publishers must be complimented for the general appearance of the book, as well as the accurate reproduction of the photomicrographs. We wonder if a discussion of the lymphatic system draining the oral tissues would not have been an appropriate addition to the book.

We heartily recommend this Oral Histology and Embryology to the student and practitioner alike.

H. C.

HISTORY OF MINERS' DISEASES. By GEORGE ROSEN, M.D. Introduction by HENRY E. SIGERIST, M.D. Pp. 490; many figures and tables. New York: Schuman's, 1943. Price, \$8.50.

THE seven years spent by the author in the preparation of this monograph have been well rewarded. His purpose of presenting "a comprehensive historical study of miners' diseases from prehistoric times to the end of the 19th century" has been well fulfilled, so that the student of the subject will find much solid information—both historical, sociologic and economic—while the more casual reader will find considerable entertainment. The latter will find more of interest in the first third of the book—Part 1, From Neolithic Times to the End of the 18th Century, and may be pardoned for skipping long stretches of Part 2, especially the often dreary analyses of relatively unimportant reports included in the 170 pages of Pathology and Nosography. Dr. Rosen has rightly decided that (in Sigerist's introductory words) "The history of occupational diseases is infinitely more than medical history," and that, here especially, "whether any use was made of medical knowledge did not depend so much on the physicians, as on the social organization under which the laborer performed his work." There are important chapters, therefore, on Mining and Miners, Morbidity and Mortality Statistics, The Beginnings of Social and Protective Legislation, as well as on the more strictly medical aspects.

One's regret that the study stops with the end of the 19th century, and

thus incidentally includes nothing about American mining, is tempered by the author's expressed hope that, under more propitious circumstances, he will present a similar study of the first four decades of the 20th century. At that time, also, he can cover asbestosis, silicosis, miner's nystagmus, miner's anemia and cancer of the lung, as adequately as he has presented anthracosis in this volume.

One wishes, too, that such a well-prepared book could have been more lavishly illustrated. The 8 illustrations from Agricola's *De Re Metallica* might have set a standard that would have at least tripled the number of the fascinating 3 pre-Agricola pictures, and quadrupled those of the later period. Certainly the 2 pictures taken from Snell and from the Report of the Royal Commission of 1842 tell more vividly and emphatically than pages of text, the need at that time for drastic change. They should make us, too, more understanding and therefore more tolerant of organized labor's present abuse of its opportunities, now that it is having its innings.

As a final recommendation of this and similar efforts, when well done, we may quote Sigerist's final paragraph: "The historical presentation of a problem that has been solved is interesting enough because it illustrates the long way that had to be gone before the goal was reached. But when a job is not finished then the historical analysis becomes the more significant. By revealing the factors involved, those that retard and those that accelerate developments, it helps us to act more intelligently and thus paves the way into the future."

E. K.

TEXTBOOK OF ANATOMY AND PHYSIOLOGY. By CATHERINE PARKER ANTHONY, B.A., R.N., Instructor of Anatomy and Physiology, Lutheran Hospital, Cleveland, Ohio; Formerly Instructor of Anatomy and Physiology, Frances Payne Bolton School of Nursing, Western Reserve Univ. Pp. 400; 35 tables; 153 illus. (8 color plates). St. Louis: C. V. Mosby, 1944. Price, \$3.50.

This textbook in Anatomy and Physiology intended for preclinical nursing students is planned for a course of 90 to 100 hours. The text presents the essentials of anatomy and physiology, using a plan which conserves the instructor's time in preparation and facilitates the student's learning. The topical outlines preceding each chapter develop the subject matter in a logical way by the use of clear tables, diagrams and pictures. A compact outline summarizes each chapter. Stimulating review questions follow. Prepared examinations for each chapter and an answer key are also provided.

This text is a valuable contribution to nursing education, being especially adaptable to the school of nursing with a limited teaching personnel. While not planned for a reference or research book, it contains all the essential concepts of anatomy and physiology necessary for preclinical students.

H. F.

SYNOPSIS OF DISEASES OF THE HEART AND ARTERIES. By GEORGE R. HERRMANN, M.S., M.D., Ph.D., F.A.C.P., Professor of Medicine, Univ. of Texas; Director of the Cardiovascular Service, John Sealy Hospital Consultant in Vascular Diseases, U. S. Marine Hospital. Third ed. Pp. 516; 103 figs.; numerous tables; 103 illus. (4 color plates). St. Louis: C. V. Mosby, 1944. Price, \$5.00.

This handbook of cardiovascular diseases has been useful and popular. It demonstrates well how a large body of information can be presented in a concise and easily understandable manner. These characteristics have been retained in the 3rd edition. There have been some rearrangements made and new sections added which are pertinent to this field in relation to the war. Such are a description of the immersion foot syndrome, and a chapter on Military Cardiovascular Examinations and Interpretations. Of considerable interest, also, is an Appendix which describes new electrocardiographic data obtained with the use of unipolar central terminal precordial leads. The illustrations throughout the book are excellent. The pressure of accelerated

teaching programs will undoubtedly enhance the value of this book to teachers and students. The busy practitioner will find it helpful in clarifying some of the problems with which he is faced. L. A.

PHYSICAL BIOCHEMISTRY. By HENRY B. BULL, PH.D., Associate Professor of Physiological Chemistry, Medical School of Northwestern Univ. Pp. 347; 93 figs.; 44 tables. London: Chapman & Hall; New York: John Wiley & Sons, 1943. Price, \$3.75.

It is sometimes the pleasure of a Reviewer to be, in essence, an advertiser, albeit one whose sincerity may by the very nature of things be taken for granted. So it is that in this case the Reviewer, having found himself a whit less ignorant for the study of his subject, would urge his fellows to do the same.

Dr. Bull has here presented the working methods of thought of one of the most basic sciences, without whose language at the very least the modern investigator is increasingly helpless and limited. The derivations are presented rather in outline than in full, but ample references are supplied. This has the virtue of allowing a book of moderate length to survey a vast field. Some may find grounds for criticism when highly complex mathematical equations are introduced "out of the blue," or adjacent to simpler ones. Since such equations are uniformly pertinent and necessary to the subsequent discussion, the reader has the choice of accepting what is given or following it out in the literature. In the chapter on electrostatics, Poisson's equation for the relation between potential and charge is an example. It is the Reviewer's feeling that this limitation is inherent in the outline, or survey method of discussion, and needs no defense. It may further be held that many surveys, by their brevity, leave nothing applicable in their wakes; Dr. Bull steers skilfully between the Scylla of sketchiness and the Charybdis of unwieldly length, leaving the reader with an extremely useful system of thought, some knowledge of experimental method, and one of the best bibliographies in the field.

It lends concreteness to the discussion and orients the prospective reader to glance briefly at some of the material covered. A preliminary discussion of atomic structure leads to a consideration of isotopes, molecular structure and the nature of chemical bonds. The section on thermodynamics wisely emphasizes the practice of dimensional analysis of equations, and then leads off with a simple and useful presentation of entropy, an understanding of which is so often difficult for the student. The subsequent development of the expressions for energy change and activities is easily followed and of immediate applicability to biologic problems. The chapter on reaction kinetics leads into the heart of quantitative biologic measurements with a thorough discussion of reactions catalyzed by enzymes. The section on dielectrics reviews a field complex in nature, and difficult of discussion, which is vital to structural organic chemistry. In this case, the reader must be tolerant enough, if critical of the brevity, to remember the purpose of the book; sufficient material is presented for the understanding of subsequent sections. The highlight of the chapter on ions in solution is an able development of the Debye-Huckel theory of interionic attraction, called by the author one of the most important contributions to chemistry in this century.

It must suffice merely to mention some of the remainder of the 18 chapters. These include discussions of acids and bases, oxidation-reduction, electrokinetics (with a clear explanation of electrophoretic techniques), interfacial problems, colloidal solutions, membranes, and other related subjects.

There is throughout the book a sense of well-disciplined thought and exacting analysis which leaves the reader well grounded for further and more detailed study, and well fitted for the critical improvement of his own experimental approach. As a scientist of extensive training and experience, Dr. Bull gives here the tools with which the exact investigator may vastly improve himself. If he be already conversant with physical chemistry, he will find new order and clarity for his mental workshop—if not, he will search long and far for a better introductory course. B. R.

MOTIVATION AND VISUAL FACTORS. By IRVING E. BENDER, HENRY A. IMUS, JOHN W. M. ROTHNEY, CAMILLA KEMPLE, and MARY R. ENGLAND. Pp. 369. Dartmouth Coll. Pubs., 1942. Price, \$4.00.

COMPLETE visual examinations were made during the 4 years of the college course on students entering Dartmouth University beginning with the fall of 1936. Data of psychologic factors and motivation were obtained during the students' senior year by interviews, autobiographies, projective techniques and so forth. On the basis of these varied data, a detailed presentation is made of the motivational pattern of 20 representative students under various visual classifications in order to show the relevance of the visual factor in the light of the total personality. For each case there is given a summary of the general data, a visual summary, a psycho-portrait of the student, and finally a brief description of the rôle of the visual factors, in view of the motivational structure of the individual. The authors point out that their results must be interpreted as being restricted to the special population studied, for among Dartmouth students visual handicaps are rare, and none of those who were examined were functionally handicapped to any considerable degree. Further, all those who needed glasses were provided with adequate correction. It is further pointed out that the results obtained are only a contemporary study of motivation, since no attempt was made to study the influence of the visual defects upon motivation in the early life of the individual.

The authors conclude that it is not possible to draw any conclusion regarding the influence of visual defects on the motivational pattern of the individual. However, the evidence does indicate that the motivational pattern of the individual influences his adjustment to his visual condition. The findings indicate that it is important to correct visual defects which interfere with visual comfort and with the visual efficiency of the subject. This book is of far more interest and importance to those who are concerned with the psychologic background of the students than with the visual defect. F. A.

THE GENEALOGY OF GYNÆCOLOGY. History of the Development of Gynæcology Throughout the Ages, 2000 B.C.-1800 A.D., with excerpts from the many authors who have contributed to the various phases of the subject. By JAMES V. RICCI, A.B., M.D., Associate Clinical Professor of Gynecology and Obstetrics, New York Medical Coll.; Director of Gynecology of the City Hospital, New York; Associate Attending Gynecologist and Obstetrician, Flower and Fifth Avenue Hospitals, New York; Consultant in Gynecology and Obstetrics, Broad St. Hospital; Fellow of the New York Academy of Medicine. Pp. 578; 54 figs. Philadelphia: Blakiston, 1943. Price, \$8.50.

A COLLEAGUE who knows medical history, having been asked recently where he would place the chronologic mid-point of medical history, *i. e.*, the data which would divide medical progress into two equal halves, answered, "Oh, about 50 years ago." We both were sure that such a date would fall on this side of the year 1800. If either of these is correct, a survey, such as Ricci's Genealogy, misses half or more of the story. In fact, it would be hard to accept, if one did not see the Footnote on p. xviii of Dr. Schumann's Introduction, telling us that a second volume on modern gynecology was to follow.

This, said, one can be free with praise of this full, well-documented narrative, modestly told, but clearly representing years of patient labor that doubtless would have been laborious if it were not, as is obvious, a labor of love. The author, a teacher and practitioner of gynecology and obstetrics, more than an historian, makes no pretense at original research, and "as a child in scholarship" has "leaned heavily on the monumental compilations of the master, medical historians," as may be verified in the character of the references. In fact, one might add that volumes such as this, directed at the reader who is not a professional historian himself, possesses certain advantages when not composed by the professional historian; and there are practically no medical histories in English, general or special, by professional medical histor-

ians, anyhow; on gynecology and obstetrics, Jameson's small volume in the Clio-Medica Series is the only one I know of in English.

The author follows the conventional chronologic approach: The Prehistoric Period; The Ancient Epoch (Egyptian, Babylonian, Assyrian, Hindu, Hebrew); The Classic Age; The Byzantine Period; The Arabic Era; The Mediaeval Epoch; The Transitional Period (Renaissance, 17th and 18th centuries)—a part about as long as all the preceding parts together. An Index of 64 double columns in small print shows the detailed and conscientious way in which this book had been prepared; and yet the Subject Index (of 12 columns) could well be much larger still. The Index of Personal Names shows how many past writers can be found here, and only here among medical histories.

The references are conveniently placed for the reader at the bottom of each page, in addition to a Bibliography at the end of each chapter. They not infrequently, however, refer to a translator or commentator rather than to the original source, or may not be sufficiently "complete" to lead to the source, without further search; the names of authors of Latin works may be misspelled or appear in the genitive case, errors of typography are more than average. These are but minor criticisms, however, and we know of no other history of this subject in English that compares with this work in its fulness, yet readability, its richness of illustrations, its documentation, and its guides to further reading. For the clinician and layman aware of medico-historical values, this narrative is highly recommended; for all, it is a valuable reference work that leads to a rich list of sources.

E. K.

THE COMPLETE PEDIATRICIAN. By W. C. DAVISON, Professor of Pediatrics, Duke Univ. School of Medicine; Formerly Acting Pediatrician in Charge, The Johns Hopkins Hospital. Fourth ed. Durham, N. C.: Printed by Seeman Printery for Duke Univ. Press, 1943. Price, \$3.75 by check; \$4.00 on credit.

"This 4th edition, in which 7000 lines were changed, was written because of the accumulation of additional pediatric information during the past 3 years, particularly in chemotherapy, infectious and tropical diseases . . ." This well-known handbook now contains 13 chapters divided into a total of 250 sections, and a score of orderly, helpful tables. The first 7 chapters are composed of organized lists of the symptoms and signs produced by diseases of the major organ systems, with notes on the diseases and on treatment. The remaining chapters discuss laboratory and other procedures frequently used in pediatrics; nutritional requirements; feeding and diets; therapy and pediatric nursing; growth, development and child care; history taking and physical examination; and drugs and prescriptions. There are innumerable cross-references.

The author deems lactic acid milk the optimal base for artificial infant feeding. Planned for "medical students, internes, general practitioners and pediatricians," the book is a comprehensive summary of facts pediatric, judiciously compiled and easy to use.

I. W.

NEW BOOKS

Tuberculosis of the Ear, Nose, and Throat: Including the Larynx, the Trachea, and the Bronchi. By MERVIN C. MYERSON, M.D. Dedication to DR. HUBERT ARROWSMITH, Pioneer in Bronchoscopy and Laryngology. An outstanding worker in the field of tuberculosis. Pp. 291; 89 figs. Springfield, Ill.: Charles C Thomas, 1944. Price, \$5.50.

This should be in the hands of all who work with institutional tuberculous patients and is of value to all who practice otolaryngology. The Author has presented the subject in a clear, concise, yet adequately comprehensive manner. Diagnostic and therapeutic procedures are discussed in detail. The book is well illustrated and contains an excellent bibliography.

K. H.

Psychiatry and the War. A Survey of the Significance of Psychiatry and Its Relation to Disturbances in Human Behavior to Help Provide for the Present War Effort and for Post War Needs. Edited by FRANK J. SLADEN, M.D., Physician-in-Chief, Henry Ford Hospital, Detroit Trustee, McGregor Fund. Contributions of the Conference on Psychiatry of the University of Michigan and McGregor Fund. Pp. 505. Springfield, Ill.: Charles C Thomas, 1943. Price, \$5.00.

Experimental Spectroscopy. By RALPH A. SAWYER, PH.D., Professor of Physics, University of Michigan. Now Lt. Comdr., U.S.N.R. and on leave from the Univ. of Michigan. Pp. 323; 107 figs. New York: Prentice-Hall, 1944. Price, \$6.00.

Infections of the Peritoneum. By BERNARD STEINBERG, M.D., Director of Toledo Hospital Institute of Medical Research; Past Fellow of the National Research Council; Former Crile Research Fellow, Western Reserve Univ. Foreword by FREDERICK A. COLLIER, M.S., M.D., Professor of Surgery, Univ. of Michigan Medical School; Director, Dept. of Surgery, University Hospital, Ann Arbor, Mich. Pp. 455; 45 figs.; 21 tables. New York and London: Paul B. Hoeber, 1944. Price, \$8.00.

Caesarean Section. The History and Development of the Operation From Earliest Times. By J. H. YOUNG, M.B., CH.B., D.T.M. and H. (EDIN.). Foreword by MILES H. PHILLIPS, M.D. (HON.), B.S., F.R.C.S., F.K.C.O.G. Pp. 254; 22 tables. London: H. K. Lewis, 1944. Price, 16 Shillings.

Principles and Practices of Inhalational Therapy. By ALVAN L. BARACH, M.D., Associate Professor of Clinical Medicine, Columbia Coll. of Physicians and Surgeons; Assistant Attending Physician, Presbyterian Hospital. Pp. 315; 59 figs. Philadelphia: J. B. Lippincott, 1944. Price, \$4.00.

Physical Medicine in General Practice. By WILLIAM BIERMAN, M.D., Attending Physical Therapist, Mount Sinai Hospital; Assistant Clinical Professor of Therapeutics, New York Univ. Medical Coll., New York. Pp. 643; 310 figs. New York and London: Paul B. Hoeber, 1944. Price, \$7.50.

Hydronephrosis and Pyelitis (Pyelonephritis) of Pregnancy. Etiology and Pathogenesis. An Historical Review. By H. E. ROBERTSON, M.D. Philadelphia: W. B. Saunders, 1944. Price, \$4.50.

The Neurosurgical Patient. His Problems of Diagnosis and Care. By CARL W. RAND, Clinical Professor of Neurological Surgery, Univ. of Southern California, School of Medicine, Los Angeles, Calif. Pp. 576; 121 figs. Springfield, Ill.: Charles C Thomas, 1944. Price, \$4.00.

Secretory Mechanism of the Digestive Glands. By B. P. BABKIN, M.D., D.Sc., LL.D., F.R.S.C., Research Professor of Physiology, McGill Univ., Montreal, Canada; Formerly Professor of Physiology in the Univ. of Odessa, Russia, and in Dalhousie Univ., Halifax, Nova Scotia, Canada. Dedication to DR. CHARLES F. MARTIN, Emeritus Dean of Medical Faculty of McGill Univ. Pp. 900; 220 illus. New York and London: Paul B. Hoeber, 1944. Price, \$12.75.

The Electrocardiogram. Its Interpretation and Clinical Application. By LOUIS H. SIGLER, M.D., F.A.C.P., Attending Cardiologist and Chief of Cardiac Clinics, Coney Island and Harbor Hospitals; formerly Instructor in Medicine, New York Post-Graduate Medical School, Columbia Univ. Pp. 403; 203 illus. and plates. New York: Grune & Stratton, 1944. Price, \$7.50.

Artificial Pneumothorax in Pulmonary Tuberculosis. Including Its Relationship to the Broader Aspects of Collapse Therapy. By T. N. RAFFERTY, M.D., Phoenix, Ariz. Formerly Resident Physician, William H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Mich. Introduction by HENRY STUART WILLIS, M.A., M.D., Supt. and Medical Director, William H. Maybury Sanatorium, Northville, Mich. Pp. 192; 26 illus. New York: Grune & Stratton, 1944. Price, \$4.00.

The Pathogenesis of Tuberculosis. By ARNOLD R. RICH, M.D., Associate Professor of Pathology, The Johns Hopkins Univ. School of Medicine, Baltimore, Md. Pp. 1008; 89 figs.; 4 charts; 20 tables. Springfield, Ill.: Charles C Thomas, 1944. Price, \$10.50.

The Analysis and Interpretation of Symptoms. Edited by CYRIL M. MACBRYDE, M.D., and 10 contributors. Reprinted from *Clinics*, April, 1944, vol. II, No. 6. Pp. 1343 to 1644; numerous figs., tables and plates. Philadelphia: J. B. Lippincott, 1944. Price, \$4.00.

The Medical Clinics of North America. New York Number. Symposium on Psychosomatic Medicine. By 18 contributors. Pp. 787; 62 figs. Philadelphia and London: W. B. Saunders, 1944.

NEW EDITIONS

American Men of Science. A Biographical Directory. Edited by JACQUES CATTELL. Seventh Ed. Pp. 2003. Lancaster, Pa.: The Science Press, 1944. Price, \$14.00.

Colorimetric Determination of Traces of Metals. By E. B. SANDELL, Ph.D., Assistant Professor of Analytical Chemistry, Univ. of Minnesota, Minneapolis, Minn. Vol. 3. Pp. 487; 73 figs.; 66 tables. New York: Interscience Publishers, 1944. Price, \$7.00.

The Diabetic Life. Its Control by Diet and Insulin. A Concise Practical Manual for Practitioners and Patients. By R. D. LAWRENCE, M.A., M.D., F.R.C.P. (LOND.), Physician-in-charge of Diabetic Department, King's College Hospital; late Chemical Pathologist and Lecturer in Chemical Pathology, King's College Hospital. Thirteenth ed. Pp. 228; 18 figs. Philadelphia: Blakiston Company, 1944. Price, \$4.00.

Principles and Practice of Ophthalmic Surgery. By EDMUND B. SPAETH, M.D., Professor of Ophthalmology in the Graduate School of Medicine of the Univ. of Pennsylvania, Philadelphia; Attending Surgeon, Wills Hospital; Consultant in Ophthalmology, Philadelphia Hospital for Insane (Byberry); Assistant Ophthalmologist in the Rush Hospital, Philadelphia. Third ed. Pp. 934; 798 figs.; 6 color plates. Philadelphia: Lea & Febiger, 1944. Price, \$11.00.

THE fact that a new edition was necessary just 3 years after the publication of the 2nd edition, is added testimony to the popularity and value of this work. The new additions include a discussion on the physiology of squint and a clarification of the section on ptosis. The illustrations, print and binding are excellent. F. A.

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ORIGINAL ARTICLES

STUDIES ON THE MECHANISM OF THE HYPOTENSIVE EFFECT OF SUBSTANCES ELICITING LEUKOCYTOSIS AND FEVER

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AND

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MANY clinical states that produce fever and leukocytosis are followed by sustained reduction of elevated arterial blood pressure in patients suffering from hypertension. Some of these are major surgical operations (Volini and Elaxman²⁰), pneumonia, sterile or infected abscesses, non-shocking burns¹⁹ and "non-specific" protein reactions. It was inevitable that this latter type of reaction should be considered in relationship with the lowering of blood pressure of hypertensive patients and animals that follows injections of kidney extracts, such as were described by Grollman, Williams and Harrison⁶ and workers in this laboratory.^{11,12,13} In a progress report concerning reduction of blood pressure with kidney extract, Page, Helmer, Kohlstaedt, Kempf, Corcoran and Taylor¹⁴ stated that, "Almost nothing is known concerning the manner in which kidney extract lowers blood pressure," and that, "Pyrogenic and local tissue reaction may contribute to the lowering of blood pressure in some patients but it appears unlikely to be the chief cause." The work of Rodbard and Katz¹⁷, who observed greater reduction of the blood pressure of hypertensive dogs with abscesses following implantation of kidney tissue, than animals with similar lesions produced by implants of other tissue, would seem to substantiate this feeling. More recently Remington, Cortland, Drill and Swingle¹⁶ have demonstrated that reduction of arterial pressure of rats by extracts of kidney occurs without the participation of fever.

On the other hand, several investigators have suggested that these results were due entirely to "non-specific" reactions and have discounted any specific hypotensive qualities of kidney extracts. Thus Chasis, Goldring and Smith² found the blood pressure of hypertensive patients decreased during the reaction to intravenous injections of typhoid vaccine. They observed equally great falls in pressure when the rise in temperature was prevented by administering large doses of

aminopyrine. Schales, Stead and Warren¹⁸ reduced arterial pressure by intramuscular injections of a kidney extract whose proteins were denatured by treatment with sulfuric acid. Prinzmetal, Alles, Margoles, Kagland and Davis¹⁵ obtained similar results with heat-inactivated tyrosinase. All of these workers felt their results were due to "non-specific" protein reactions but, save for the elimination of fever as a cause by Chasis, Goldring and Smith,² no attempt was made to determine by what mechanism such reactions might reduce arterial pressure in hypertension. Without raising the question of specific blood pressure reducing qualities of kidney extract, still an explanation of the mechanism of pyrogenic hypotension is needed.

Reactions of this type are usually accompanied by a rise in the W.B.C. count due to granulocytosis. The fact that granulocytes are known to contain large amounts of histamine, a hypotensive agent, as well as proteolytic enzymes, led us to consider the possibility of a relationship between pyrogenic leukocytosis and the effects of pyrogens on arterial blood pressure. The present study was undertaken to ascertain whether or not leukocytosis as such causes a decrease in the elevated arterial pressure of experimental renal hypertension in dogs and malignant hypertension in human beings.

Methods. The dogs were made hypertensive by the silk perinephritis method of Page.¹⁰ Blood pressure was measured daily by direct intra-arterial puncture of the femoral artery. The dogs were not studied further unless the mean pressure on 10 or more successive days was stabilized above 160 mm. Hg.

In one procedure, sterile abscesses were produced by injecting 1.5 to 2.5 cc. of turpentine into the axillary tissue of hypertensive and normal animals. For another, pus from these lesions was then aspirated and injected subcutaneously and intraperitoneally into hypertensive dogs. Each of these animals received 40 to 60 cc. of sterile pus daily. In a third series the leukocyte-producing factor of necrotic tissue described by Menkin, Kodish and Warren⁸ was prepared by Dr. O. M. Helmer. Ten to 20 cc. of this material was injected subcutaneously or intravenously into hypertensive animals. The change in W.B.C. counts was followed by counting the leukocytes in heparinized blood drawn from the femoral vein. In a fourth series leukocytosis was produced by injecting 10 to 15 cc. of a 70% solution of acetyl methylamine intramuscularly, as suggested by Zondek and Bromberg.²³

The patients studied were terminal malignant hypertensives from the Lilly Clinic. The diagnosis of malignant hypertension was made according to the classification of Keith, Wagener and Kernohan,⁷ that is, by the demonstration of papilledema and retinal hemorrhages. The terminal state was determined by the presence of clinical uremia, or by the demonstration that renal function, as measured by the diodrast Tm, was not compatible with more than a few weeks' survival (Corcoran, Taylor and Page⁴). Blood pressures were taken as often as indicated by the auscultatory method. White blood counts were made from finger-tip blood.

The substances injected intravenously into these patients was prepared by Dr. A. A. Plentl of this laboratory. In the first series of experiments, the material used was an albumin fraction of pork blood. The serum to be fractionated was so decanted from the R.B.C. that the buffy layer of leukocytes was contained in it. To it was added an equal volume of 3 M $(\text{NH}_4)_2\text{SO}_4$ and the pH of the mixture brought to 6.5 by addition of 1 N H_2SO_4 . The precipitate was removed by filtration and discarded. The concentration of $(\text{NH}_4)_2\text{SO}_4$ in the filtrate was slowly increased from 1.5 to 2.1 M by the rotating cellophane membrane technique. The precipitated albumin was collected, dissolved in a small volume of water, and fractionally precipitated by succes-

sive adjustments of $(\text{NH}_4)_2\text{SO}_4$ concentration to 2, 2.15 and 2.4 M in a rotating membrane. The 2.4 M precipitate was separated by filtration, dissolved in distilled water, dialyzed against running tap water for 24 hours, and then against distilled water for 24 hours. The solution was made up to contain 8% protein, and sterilized by Seitz filtration. Thirty to 120 cc. of this solution was given on 18 occasions to 5 patients with malignant hypertension.

In a second series of experiments, human W.B.C. were extracted and injected intravenously into a patient with malignant hypertension. The W.B.C. were collected by suction from the buffy layer of 100 liters of human blood. Complete separation from the R.B.C. was effected by repeated centrifugation. The cells were then suspended in 3 volumes of distilled water. The suspension was stirred vigorously for 45 minutes, allowed to stand in the ice-box overnight, and again stirred for 45 minutes. Enough NaCl was then added to make a 4% solution. The mixture was dialyzed against tap water for 24 hours and filtered. The filtrate was adjusted to 2 M with $(\text{NH}_4)_2\text{SO}_4$ in a rotating cellophane bag. The precipitate was separated by filtration and dissolved in the least volume of distilled water. The filtrate was adjusted to 4.1 M with $(\text{NH}_4)_2\text{SO}_4$. This precipitate was collected and dissolved in distilled water.

These two solutions were sterilized with the Seitz filter and injected intravenously in 5 to 15 cc. amounts into a patient with malignant hypertension.

Outline of Methods Testing the Effects of Granulocytes on Hypertension

I. Hypertensive dogs:

Leukocytosis induced by:

1. Subcutaneous injection of turpentine with abscess formation.
2. Subcutaneous and intraperitoneal injection of sterile pus.
3. Intramuscular and intravenous injection of Menkin's leukocyte-producing factor.
4. Intramuscular injection of 70% acetyl methylamine.

II. Patients with malignant hypertension:

Extracts of leukocytes injected intravenously:

1. Albumin fraction precipitated from pork serum containing buffy layer of cells.
2. Extract of human leukocytes.
 - (a) Fraction precipitated by 2 M $(\text{NH}_4)_2\text{SO}_4$.
 - (b) Fraction precipitated by 4.1 M $(\text{NH}_4)_2\text{SO}_4$.

Results. Effects of Granulocytes on Hypertension. I. HYPERTENSIVE DOGS. A. Leukocytosis induced by:

1. *Subcutaneous Injection of Turpentine With Abscess Formation.* One and a half to 2.5 cc. of turpentine were injected into the axillary tissue of each of 10 hypertensive dogs. The response was much the same in all animals. Within 24 hours the site of injection was indurated, tender and hot; there were 1° to 2° F. of fever, and the blood pressure was 20 to 40 mm. below control levels. On the 2nd day, the lesion was more localized but not fluctuant. The temperature was much the same as the preceding day, but the blood pressure was 10 to 20 mm. lower. By the 3rd day, fluctuation was evident, the temperature was elevated 3° to 4° F., and the blood pressure was at normotensive levels of 110 to 130 mm. Hg. As long as the abscess was encapsulated, the fever and normotension persisted. At the end of 3 to 4 days the lesion began to discharge pus. The temperature returned to normal in 1 to 3 days but the blood pressure took 4 to 5 additional days to reach the previous hypertensive levels. During the first 3 to 4 days the dogs were slightly lethargic and showed evidence of pain;

however, they ate well and moved about normally during the entire experiment. A typical result is illustrated in Figure 1.

2. *Intraperitoneal Injection of Sterile Pus.* Sterile pus from turpentine-induced abscesses was aspirated and promptly injected into 8 hypertensive dogs. Twenty to 60 cc. were given subcutaneously, intraperitoneally, or both, for 6 to 13 days (Table 1). All animals had a rise in temperature of 1° to 3° F. during treatment. One dog developed peritonitis and died, and 1 died of malignant hypertension. These 2 animals had 10 to 40 mm. falls in arterial pressure 2 to 4 days before death, but no other animals showed reduction of blood pressure during or after treatment.

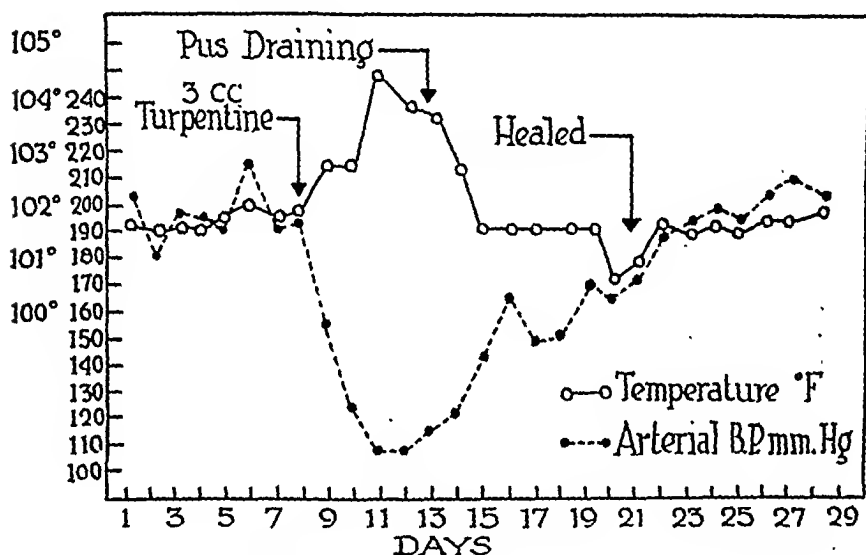


FIG. 1.—Effect of sterile abscesses on blood pressure and temperature of hypertensive dog.

3. *Intramuscular and Intravenous Injection of Menkin's Leukocyte-producing Factor.* Sterile pus was extracted for the leukocyte-producing factor of Menkin. Eight animals received 10 to 15 cc. of this extract intravenously or subcutaneously for 7 to 12 days (Table 2). The average increase of W.B.C. count was 46% (maximum 85% and minimum 28%). No variation of temperature or blood pressure was observed.

4. *Intramuscular Injection of 70% Acetyl Methylamine.* Eight dogs were given daily injections of 10 cc. of a 70% solution of acetyl methylamide for 5 to 13 days (Table 2). The average rise in W.B.C. was 66.4% (maximum 134% and minimum 25%). One dog developed an abscess at the site of injection and experienced a fall in blood pressure similar to those that received turpentine. Another animal was given 20 cc. of the 70% solution on 2 successive days and died of massive hemorrhage from the urinary and respiratory tracts. Autopsy indicated advanced liver necrosis with fatty infiltration. Otherwise there were no untoward results, and neither fever nor hypotensive effects were recorded.

TABLE 1.—EFFECT ON ARTERIAL BLOOD PRESSURE OF HYPERTENSIVE DOGS RECEIVING INJECTIONS OF STERILE PUS

Dog No.	Amount given (cc. each day)	Route given	Before			Receiving injections			After		
			Av. B.P. (mm. Hg)	Av. body temperature (° F.)		Av. B.P. (mm. Hg)	Av. body temperature (° F.)	Days observed	Av. B.P. (mm. Hg)	Av. body temperature (° F.)	Days observed
1	40	Intraperitoneally	204	101 ^s		206	102 ^s	7	200	102	10
2	20	Subcutaneous	201	101 ^e		202	102 ⁴	7	207	101 ⁴	6
3	40	Intraperitoneally	207	101 ^s		210	103 ^s	10	200	101 ^s	6
4	20	Intraperitoneally	199	101 ^e		186	104 ^s	9	180	101	9
5	40	Subcutaneous	186	102 ^s		166	102 ^s	13	168	101 ^s	10
6	40	Intraperitoneally	197	101		192	101 ^e	5	Died of malignant hypertension		
7	50	Intraperitoneally	207	101 ^e		213	102 ⁴	8			
8	60	Intraperitoneally	210	101 ^e		198	102 ^s	8	196	101 ^s	10
Averages	38.7	...	201.4	101 ^e		196.6	102 ⁷	...	191.8	101 ^s	

TABLE 2.—LEUKOCYTOSIS INDUCED IN HYPERTENSIVE DOGS BY INTRAMUSCULAR INJECTIONS OF 70% ACETYL METHYLAMINE

No.	Before					Receiving injections					After				
	Days observed	Av. mean B.P. (mm. Hg)	Av. white cells per c.mm. blood	Av. temperature (° F.)	Amount injected daily (cc.)	Days observed	Av. mean B.P. (mm. Hg)	Av. white cells per c.mm. blood	Increase in WBC (%)	Av. temperature (° F.)	Days observed	Av. mean B.P. (mm. Hg)	Av. white cells per c.mm. blood	Av. temperature (° F.)	
1	14	190	18,940	101 ²	8	13	180	23,790	26	101	8	184	16,050	101	
2	17	185	12,460	101 ⁴	10	6	176	17,420	40	101 ⁴	14	188	9,840	101 ⁴	
3	17	181	10,600	102	10	9	182	18,810	77	101 ⁸	14	191	11,210	101 ⁸	
4	15	204	14,630	101	12	9	198	34,300	134	100 ⁶	10	194	15,200	100 ⁸	
5	14	197	24,200	100 ²	15	5	182	35,600	46	100	Died from hemorrhage				
6	14	161	12,510	100 ⁴	10	6	154	26,080	108	100 ³	14	158	12,620	100 ⁴	
7	14	185	13,525	100 ⁷	12	5	185	20,400	50	101	Died—malignant hypertension				
8	15	160	14,970	100 ⁶	8	13	140	22,460	50	102 ⁴	14	158	16,210	100 ⁷	
Abscess at injection site															
Av.	15	182.8	15,230	100 ⁹	10.6	8.25	174.6	24,860	66.4	101 ¹	12.3	178.8	13,520	101	

LEUKOCYTOSIS INDUCED IN HYPERTENSIVE DOGS BY INTRAMUSCULAR INJECTIONS OF MENKIN'S LEUKOCYTE-PRODUCING FACTOR														
1	14	162	9,780	100 ²	10	7	155	13,740	40	100 ⁶	10	156	13,460	100 ⁶
2	14	161	16,000	101 ⁴	12	7	165	23,385	46	101 ⁶	10	164	13,820	101 ⁶
3	10	162	16,700	101 ²	15	6	166	21,300	28	101 ²	10	171	12,100	101
4	14	165	12,540	101 ⁶	15	8	165	17,830	42	101 ⁴	14	160	11,315	101 ⁴
5	14	160	15,525	101 ⁵	12	9	160	21,480	40	101 ⁶	14	165	11,420	101 ⁴
6	14	165	12,510	101 ³	15	12	172	19,560	56	101 ⁶	14	174	12,370	101 ⁴
7	11	243	36,060	101 ⁴	15	9	221	47,190	31	102 ²	Died—malignant hypertension			
8	12	182	21,920	102	20	8	184	40,500	85	101 ³	12	185	19,650	101 ³
Av.	12.8	175	17,630	101 ³	14.25	8.25	173.5	25,620	46	101 ⁵	12	167.8	13,450	101 ³

TABLE 3.—EFFECT OF EXTRACT OF PORK SERUM CONTAINING BUFFY COAT ON ARTERIAL BLOOD PRESSURE OF MALIGNANT HYPERTENSIVES

Patient	Amount given (cc.)	Route of administration	Reduction of B.P. 1 to 4+	Duration of reduced B.P.	Type of reduction		Evidence of allergy 1 to 4+	Post-treatment temperature (° F.)	WBC per c.mm. blood	
					Immediate	Delayed			Before treatment	After treatment
1	50	Intravenous	+++	40 min.	+	..	++	98°	6,520	15,200
2nd day	100	Subcutaneous	98°	10,800	14,800
3rd day	50	Intravenous	+++	12 min.	+	...	+++	102°	6,750	16,750
2	50	Intravenous	+++	25 min.	+	...	+++	98°	7,850	14,800
3	50	Intravenous	+++	20 min.	+	...	+	102°	10,600	25,200
2nd day	50	Intravenous	+++	7 min.	+	...	+	101°
3rd day	80	Subcutaneous	102°	25,800	22,650
4	60	Intravenous	+++	12 hrs.	...	+	++	101	8,700	18,600
2nd day	30	Intravenous	+	101	18,600	19,200
3rd day	30	Intravenous	99	18,400	23,600
4th day	30	Intravenous	99°	23,600	26,200
5	80	Intravenous	++	12 hrs.	...	+	++	Pretreatment aminopyrine	9,200	29,000
2nd day	16	Intravenous	++	98°	29,000	25,000
3rd day	30	Intravenous	++	99°	25,000	12,800
4th day	28	Intravenous	++	12 hrs.	...	+	+++	99°	12,800	10,600

EFFECT OF EXTRACTS OF HUMAN WHITE CELLS ON ARTERIAL BLOOD PRESSURE OF PATIENTS WITH MALIGNANT HYPERTENSION

Patient	Amount given (cc.)	Route of administration	Reduction of B.P. 1 to 4+	Duration of reduced B.P.	Type of reduction		Evidence of allergy 1 to 4+	Post-treatment temperature (° F.)	WBC per c.mm. blood	
					Immediate	Delayed			Before treatment	After treatment
1	18	Intravenous	+++	12 hrs.	...	+	+++	98°	6,250	19,700
2nd day	10	Intravenous	+++	100	19,700	26,800
2	5	Intravenous	+++	102	9,500	42,500

Extract No. I

Extract No. II

II. PATIENTS WITH MALIGNANT HYPERTENSION. A. Extracts of leukocytes injected intravenously:

1. *Albumin Fraction Precipitated From Pork Serum Containing Buffy Layer of Cells.* An 8% solution of this material was given intravenously on 15 occasions to 5 patients with malignant hypertension. In 3, arterial pressure fell rapidly and remained low for intervals of 25 to 40 minutes. Repetition of the injection 24 hours later produced less marked and less sustained falls in pressure. Each injection was accompanied by evidence of allergic reaction, such as hives, nausea, involuntary defecation and fever. Twenty-four hours after treatment all cases showed leukocytosis, but blood pressure continued at the usual hypertensive levels (Table 3).

On 3 occasions, in 2 patients, the fall in arterial pressure was delayed, occurring 6 to 10 hours after the injection and lasting about 2 hours. However, each was accompanied by evidences of sensitization and could not be reproduced by subsequent injections. These 2 patients maintained pretreatment hypertensive levels in the face of 200% increases of leukocyte count on the days following the treatment (Table 3).

Subcutaneous injections of the material caused no changes in arterial blood pressure.

2. *Extracts of Human Leukocytes.* (a) Fraction precipitated by 2 M $(\text{NH}_4)_2\text{SO}_4$: The injection of this fraction resulted in flushing, pain in the back, chest and joints; and blood pressure fell 100 mm. Hg systolic and 80 mm. diastolic 2 hours after, returning to previous levels within 12 hours, at which time there was a 200% increase in white cell count.

The fall in blood pressure could not be duplicated in this patient 24 hours later, but the evidences of allergic sensitivity were again manifest and the W.B.C. rose to 400% of its normal level.

(b) Fraction precipitated by 4.1 M $(\text{NH}_4)_2\text{SO}_4$: Injection of the second fraction of the washed human leukocytes on 1 patient resulted in hives, perspiration, fever and a 42,500 W.B.C., but without accompanying change in arterial blood pressure.

Discussion. This report is a part of an investigation undertaken to determine the mechanism whereby "non-specific" and inflammatory reactions cause reduction of arterial blood pressure in hypertensive patients and animals. The majority of such reactions are accompanied by fever and leukocytosis, both of which must be considered as having possible relationship to this change in arterial pressure; the former because it is associated with vasodilation and might thus evoke hypotension, and the latter because of the high content of histamine and proteolytic enzymes present in granulocytes. Chasis, Goldring and Smith² eliminated hyperpyrexia as the vasodilator responsible for the reduction of blood pressure in "non-specific" reactions. They blocked the temperature rise of hypertensive patients who received reaction-producing doses of typhoid vaccine intravenously by administering large doses of amidopyrine before the injection of

vaccine, and observed equally marked vasodilation, renal hyperemia and reduction in blood pressure as in febrile patients.

Our studies have eliminated leukocytosis as well as large collections of leukocytes as components in the mechanism that causes vasodilation and lowered blood pressure. Neither injections of sterile pus nor the peripheral leukocytosis that followed injection of Menkin's leukocyte-producing factor and 70% acetyl methylamine had an effect on the mean arterial pressure of hypertensive dogs. Likewise, leukocytosis and extracts of W.B.C. did not consistently lower the blood pressure of patients with malignant hypertension. The lowered pressures that were observed were clearly due to allergic reactions. In light of these findings, it seems safe to assume that neither fever nor granulocytes cause the vasodilation that occurs in inflammation and "non-specific" reactions.

This evidence, in conjunction with the observation that fresh, sterile pus which should contain any hypotensive material that might result from denaturation of tissue proteins by inflammation or proteolytic enzymes, failed to reduce blood pressure; and would seem to point to some alteration in febrile states of the homeostatic mechanism responsible for maintenance of vascular tone and elevated blood pressure. By this we mean that some humoral agent akin to those that induce leukocytosis, cellular diapedesis and fever itself, in inflammation (Menkin, Kodish and Warren⁸) may be selectively antagonistic or depressant to a body function that has to do with the maintenance of blood pressure.

Such a function could be ascribed to the adrenal cortex, inasmuch as Goldblatt,⁵ Page,⁹ Collins and Wood,³ and Blalock and Levy¹ have all demonstrated that renal hypertension is difficult to induce or sustain in adrenalectomized animals treated with salt and adrenal cortical extracts. More recently, Weil and Browne^{21,22} have demonstrated a qualitative change in adrenal cortical function as the result of systemic injury (operation, fracture, burn, febrile illness). This change is reflected in increased urinary excretion of cortin-like material with diminished excretion of 17-ketosteroids and the establishment of negative nitrogen balance. Such insults to the body economy could also depress the secretion of another adrenal factor which maintains vascular reactivity in hypertension and thus account for the decreased arterial pressure which often follows it. As other explanations of this type of hypotension fail, some such concept comes to deserve further study.

Summary and Conclusions. 1. The mechanism of reduction of arterial blood pressure of hypertensive patients following "non-specific" or inflammatory reactions is unexplained.

2. Fever has been eliminated as the etiologic agent.

3. The present studies have ruled out the second most common component of such reactions, leukocytosis, as the hypotensive agent.

4. Neither injection of sterile pus nor peripheral leukocytosis resulting from injection of Menkin's leukocyte-producing factor and 70% acetyl methylamine affects the blood pressure of hypertensive dogs.

5. It is suggested that "non-specific" and inflammatory reactions impair that function of the adrenal cortex that has to do with the maintenance of vascular reactivity and elevated blood pressures so eliciting reduction of arterial pressure.

Lucile V. Clary, R.N., contributed materially to this study.

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FURTHER STUDIES ON THE LEUKOCYTOSIS-PROMOTING FACTOR AND ON NECROSIN IN INFLAMMATORY EXUDATES*

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(From the Fearing Research Laboratory)

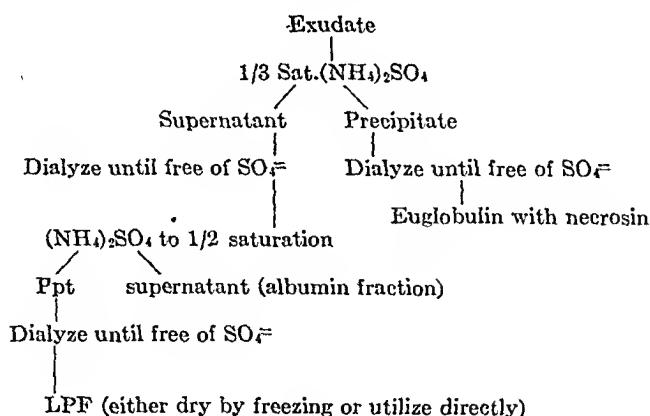
INFLAMMATION is the basic response to infectious processes.¹ As such, an important factor in its pathogenesis is a development of severe cellular injury. The inflammatory reaction is initiated by a

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disturbance in fluid exchange. It then proceeds through an orderly and fundamental pattern. The steps are in many of the sequences referable to the liberation of biochemical units liberated in turn by injured cells. Damaged cells may be regarded as having a totally different chemistry as a result of their deranged cellular metabolism. In this connection, several years ago it has been found that the mechanism of increased capillary permeability and of leukocytic migration is referable to the liberation of a crystalline nitrogenous substance recovered from exudates and termed leukotaxine.² Leukotaxine is concerned only with local migration or diapedesis of polymorphonuclear leukocytes.³ As such it fails to alter the number of circulating leukocytes when introduced into the circulation.

Leukocyte-promoting Factor. Nevertheless there seems to exist a leukocytosis-promoting factor in exudates capable of explaining the systemic leukocytosis frequently accompanying inflammatory processes, for when the exudative material is introduced into the circulating blood stream of a dog, this is followed by a rise in the number of circulating leukocytes.⁴ No such prompt response can be obtained with blood serum, bacteria, or saline. This factor is thermolabile and non-diffusible. These facts have suggested its protein nature. Indeed, fractionation with ammonium sulfate indicate that the activity is concentrated in the pseudoglobulin fraction of exudates.⁵ The present adopted scheme has been somewhat simplified:

SCHEME OF EXTRACTING THE LEUKOCYTOSIS-PROMOTING FACTOR (LPF) AND
NECROSIN FROM EXUDATES



The effect of an injection of the LPF, as we term the leukocytosis-promoting factor, is on the bone marrow, inducing a discharge of immature or non-filamentous forms of granulocytes into the circulation.⁴ I shall presently return to the question of the effect of the leukocytosis-promoting factor on the bone marrow.

The LPF is absent in normal blood serum, but it is present in the sera of animals with concomitant inflammation.⁶ Such observations and others seem to indicate that the material reaches the bone marrow by penetrating from the site of acute inflammation into the circulating blood.

The active principle is obtained readily from the exudate of man.⁷ In the first series of experiments an average increase of over 100% in the number of circulating leukocytes was demonstrated by an injection of human LPF. At present we can obtain even greater potency.⁸ These results suggest possible clinical application. The rise is essentially due to an outpouring of granulocytes. This is accompanied by an abundance of immature forms.

Recently the effect of this active biologic substance on the bone marrow has been studied.⁸ In Figure 1 the appearance of the femoral bone marrow is seen following an injection of the pseudoglobulin fraction of normal blood serum. As you note, the bone marrow appears relatively normal. Contrast this effect when only 13.5 mg. of potent LPF is injected intravenously. Two days afterwards the animal is sacrificed. Note the active growth or hyperplastic response on the part of the bone marrow (Fig. 2). This proliferative response involves primarily the granulocytic forms and the megakaryocytes.

One may conclude, then, that the existence of a leukocytosis-promoting factor in exudates offers a reasonable explanation for the mechanism of leukocytosis accompanying numerous inflammatory processes. As the prognosis of some infectious conditions has been referred to some extent to the number of circulating leukocytes,¹³ the obvious clinical implication of the LPF in reinforcing other chemotherapeutic agents deserves exploration. Finally, the prompt growth response of this material on the bone marrow may also prove to have, besides theoretical interest, clinical possibilities in various sluggish conditions of the bone marrow.

Necrosin. I now turn to another more recently identified chemico-biologic unit from inflammatory exudates. Neither leukotaxine nor the LPF induces any appreciable degree of tissue injury. Yet an inflammation is a manifestation on the part of the host of severe cellular damage. When whole exudative material is injected locally into a rabbit, a marked and appreciable response can be elicited. A search for the factor responsible for injury was undertaken. Without burdening you with too much detail, it has been found that either the euglobulin fraction or associated with that fraction of exudates, there seems to exist a factor capable of reproducing the acute injurious edematous response of inflammation.⁹ Material introduced into such an area fails to disseminate to the tributary lymphatic nodes. This is referable primarily to a lymphatic blockade, which in itself is a sign of marked local injury. Besides causing damage to the draining lymphatics, the euglobulin fraction of exudate likewise induces injury to the vascular channels in the form of small thrombi. If the factor causing injury and recovered from inflammatory exudate is a euglobulin, then it may perhaps be an atypical euglobulin; for it fails to be dissolved in the presence of electrolytes. The effect is scarcely referable to denaturation during dialysis of the $\text{SO}_4^{=}$ for an inactive fraction is obtained by similarly fractionating blood serum with $(\text{NH}_4)_2\text{SO}_4$ at one-third saturation, or sometimes by merely dialyzing whole exudative material and recovering the precipitate. Furthermore, the reason

for this statement lies in the fact that the whole exudate is injurious *per se*, inducing likewise a lymphatic blockade. No other fraction so far studied except the euglobulin fraction of exudates is capable of

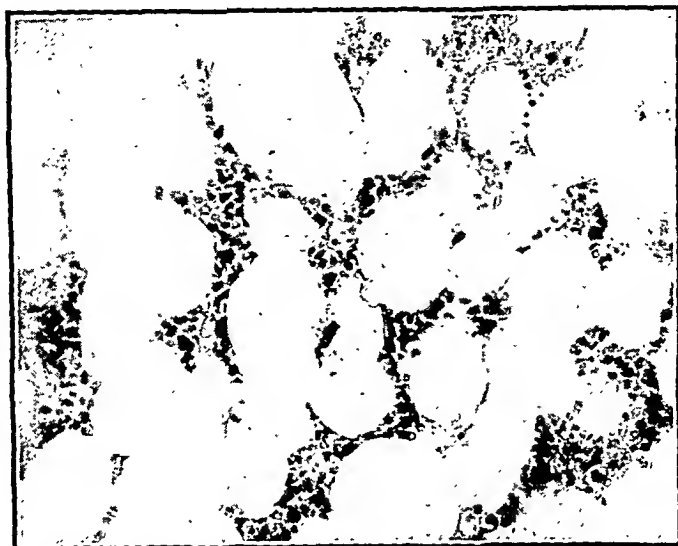


FIG. 1.—The femoral bone marrow of a dog 2 days following an intravascular injection of 14.5 mg. of pseudoglobulin derived from normal blood serum.

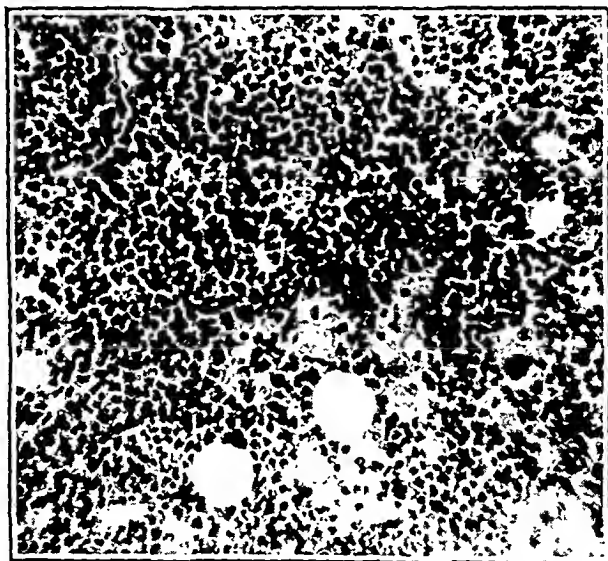


FIG. 2.—The femoral bone marrow of a dog injected 2 days previously with 13.5 mg. of leukocytosis-promoting factor. The hyperplastic response is striking. The proliferative effect involves primarily granulocytic elements and also megakaryocytes.

reproducing the acute injurious response seen in inflammation. In brief, if there is any denaturation, then that seems to be a natural phenomenon occurring *in vivo* and caused by the injured cell at the site of inflammation. For the sake of convenience this fraction of exudates

has been termed "necrosin." Its presence offers a reasonable explanation for the pattern of injury in inflammation. Now, if precisely the same procedure is repeated with non-hemolyzed blood serum, as stated above, the injected euglobulin fraction fails to display an acute inflammatory reaction with superficial necrosis, and the lymphatics remain unoccluded.

The first morphologic evidence of injury as elicited by necrosin is a swelling of the collagenous bundles. This may be found 10 minutes after intracutaneous injection of necrosin. No such effect appears upon the introduction of the euglobulin fraction obtained from normal blood serum.

Necrosin is absent in blood serum, but it is found present in the serum of an animal with a concomitant acute inflammation. Such evidence indicates that the active principle probably penetrates from the site of injury into the circulating blood stream. These observations suggest that a so-called focus of infection may indeed have far-reaching effects by liberating necrosin, which in turn penetrates into the circulation.

For this reason, observations were recorded on the effect of necrosin when introduced directly into the circulation. The animal may at first be prostrated. It may have symptoms of diarrhea and of vomiting; and, in general, the dog presents a very apathetic and listless appearance. There may be hemorrhage throughout the length of the gastro-intestinal tract. A hydrothorax involving both cavities has been encountered; but in general the constant features are injury to the liver and, very frequently, to the kidneys. The liver may show patchy areas of fatty necrosis which, on microscopic section, appear as heterogeneous zones of fat deposits interspersed among foci of leukocytic infiltration. The picture is not unlike that seen in hepatic focal necrosis. Sometimes one encounters areas of severe cellular damage in which the cell contents are replaced by a fine stippling which does not take the iron stain. The effect on the kidney is rather striking. The lumina of the tubules may show a lining with swollen, vacuolated cells having irregular contours. Interspersed are seen foci of leukocytic infiltration. The picture is not dissimilar to and, in fact, is reminiscent of a pyelonephritis.⁹

Necrosin fails to lower the blood pressure of a cat in contrast to histamine. This, however, does not necessarily mean that necrosin may not play an important rôle in traumatic shock as one of the actively participating components of the phenomenon.¹⁰

There are two other phenomena elicited by necrosin which I should like to discuss before terminating the present paper. In the first place, the injection of necrosin in contrast to the LPF induces a leukopenia.¹⁰ The blood count may fall to a level of 1000 or 2000 per c.mm. Only later the leukopenia may be replaced by a leukocytosis. This leukocytosis may well be a secondary phenomenon referable to the liberation of the LPF by organs injured in turn by necrosin. This observation may prove of real significance, for necrosin is the only fraction recovered from exudates which has been found capable of

inducing such a sharp fall in the number of circulating leukocytes. It is to be recalled, for instance, in this connection, that the pathologic picture of local vascular thrombi and leukopenia encountered in typhoid fever is reminiscent of the effects produced by the injection of necrosin. One wonders whether a number of clinical conditions with leukopenia may not be referable to the liberation of an abundant amount of necrosin at the site of inflammation. The finding that necrosin induces leukopenia has been utilized in the further purification of the LPF from exudates. Recent observations to be subsequently reported *in extenso* by Major A. Mirsky and the writer, indicate that the injury factor in necrosin contains proteolytic activity which can be at least partially neutralized by an antiprotease. These facts suggest that plerosin is a proteolytic enzyme or that it is at least associated in its present state of purification with such an enzyme. On the other hand, the pyrogenic factor in the euglobulin fraction of exudate is definitely non-proteolytic in activity.

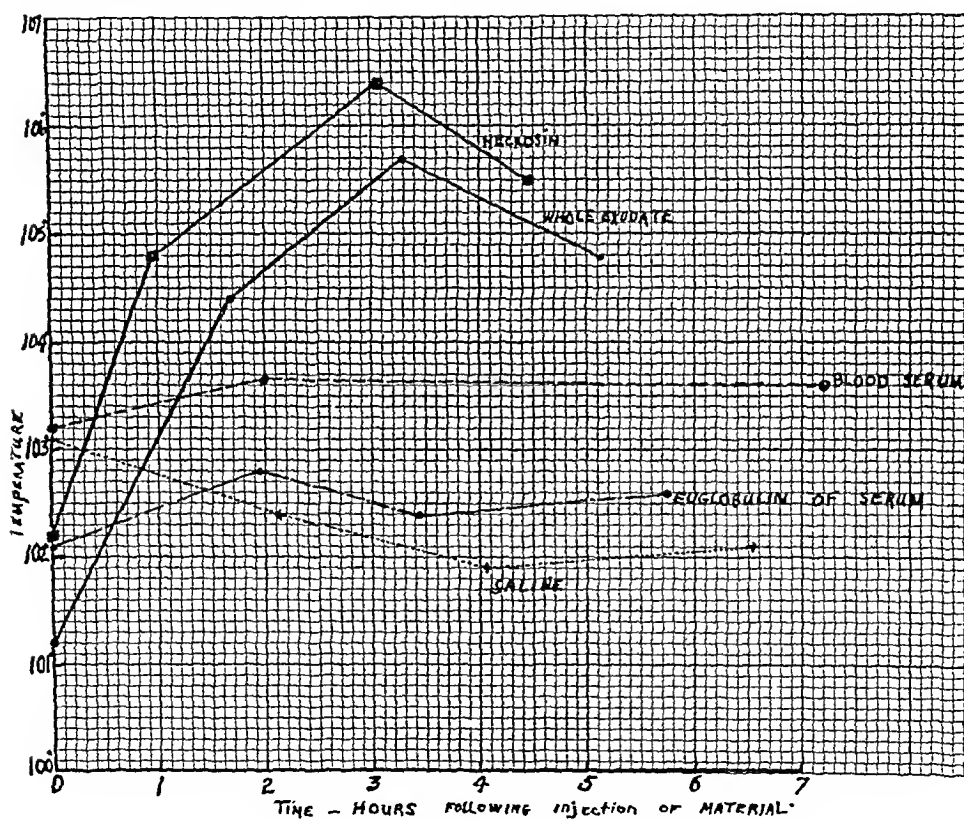


CHART 1.—The effect of necrosin and of other substances on the temperature level of the rabbit.

Finally, I should like to dwell on the effect induced by necrosin on temperature.^{9,10} Necrosin injected into a dog induces fever. The LPF or other protein fractions procured from exudates fail to do so.¹⁰ The elevation in temperature may be very marked: 3° to 5° F. Of late it has been found that the rabbit is extremely susceptible to the

effect of necrosin as regards temperature levels (Chart 1). Note that the whole exudate (or the dried exudate) induces fever. Necrosin reproduces the same effect. Hemolyzed serum does the same, whereas non-hemolyzed serum fails to do so to any appreciable effect. The significance of this finding may prove of value in determining the immediate factor involved in the onset of fever in malaria. It is conceivable that the release of the contents of red corpuscles into the circulation may likewise liberate an abundance of necrosin which in turn would be responsible for the pyrogenic effect. The evidences which are now being obtained indicate that the rabbit may prove to be a very suitable test animal for the determination of necrosin in various body fluids. Studies are now under way to determine the factor in necrosin which is responsible for the production of fever. This latter seems to be referable to a highly heat-stable component in contrast to the labile injury factor in necrosin. Studies are also in progress in an endeavor to determine if this substance acts by stimulation of the heat centers. In brief, sufficient material has been advanced in the present discussion to indicate that necrosin liberated at the site of injury in turn by penetrating into the circulating blood stream may well be responsible for the primary mechanism of fever production accompanying inflammatory processes.

Conclusion. Injured cells as encountered in inflammation display a wholly different chemistry than normal cells. By releasing various common denominators such as leukotaxine, the LPF, necrosin, glucose,¹² even possibly urea,¹² the cell in turn initially injured by any sort of irritant, be it viable or non-viable, reasonably accounts by an altered chemistry for the stereotyped reaction of inflammation.

Further studies on the purification of the leukocytosis-promoting factor from inflammatory exudates yield by a somewhat simplified procedure, a potent biologic fraction. The substance affects both cellular growth response in the bone marrow and the number of circulating leukocytes. A leukocytosis ensues in the blood stream, and a hyperplastic response on the part of granulocytes and megakaryocytes is encountered in the bone marrow following the intravascular injection of this substance.

Necrosin, associated with the euglobulin fraction, of exudates may consist of several distinct components. Two of these are particularly striking. One is concerned with cellular injury, having proteolytic enzymatic activity, while another is pyrogenic in effect. Further studies are being conducted to determine the nature of these two components. The rabbit is found to be a good test animal for the determination of necrosin in various body fluids by its susceptibility in developing fever. The studies strongly suggest that the primary mechanism of fever associated with inflammatory processes may be referable to the absorption into the circulation of the pyrogenic component of necrosin.

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STUDIES ON PALMAR SWEATING*†

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PART I. A TECHNIQUE FOR THE STUDY OF PALMAR SWEATING

STUDIES dealing with the sweat mechanism are usually handicapped by complicated techniques. A complete review of the many methods to measure sweat is given by Kuno.¹⁵ Depending upon the amount and type of perspiration to be studied the following techniques have been used in the past: (1) Respiratory chamber; (2) balances for the measurement of body weight; (3) measurement of the whole body surface, such as enclosing the body in a rubber bag; (4) measurement of one limb or a small area of the skin by enclosing the part and introducing dry air current and collecting the moisture; (5) direct observation of sweat drops by means of a skin microscope; (6) capillary tube method by inserting a capillary tube directly into a sweat duct; (7) testing for chlorides; (8) collecting the sweat directly such as with a blotting paper; (9) utilizing a galvanometer hook-up and studying the galvanic skin reaction; (10) colorimetric methods.

Colorimetric methods are most widely used in clinical medicine today, and the most popular one is the technique devised by Minor.¹⁶ This method depends upon the color reaction produced by the interaction of iodine and starch in the presence of moisture. Guttman⁹ used chinazarin as a base and obtained more satisfactory results. In the presence of sweat, a dark stain is produced and, depending upon the extent and intensity, the degree of sweating may be graded. Roth¹⁸ applied cobalt directly to the part to be tested, and in the presence of sweat the blue color faded. These methods, however, are not always reliable, since the color reaction may be modified by the humidity. Another disadvantage is that, unless photographs are taken, the records obtained lack permanency.

To overcome these objections a colorimetric technique for measuring

* Brigadier General Royal Reynolds, Kennedy General Hospital, encouraged the writing of this paper. Lieut. Morris Kaslow gave technical assistance.

† No objection to publication, Bureau of Public Relations, War Department, Washington, D. C.

palmar sweating²⁰ of the palm and finger tips has been devised. This method has the following advantages:

1. *Availability.* The materials to be used are not critical and can be obtained at any modern pharmacy. The only chemicals used are alcohol, tannic acid or potassium ferrocyanide, and ferric chloride.

2. *Economy.* Over 1000 tests can be done at less than \$.75.

3. *Objectivity.* Over 4000 tests have been graded by different observers and there is remarkable agreement in the classification. The test is a qualitative and quantitative measure of sweat.

4. *Practicability.* The test requires no elaborate equipment, leaves practically no stain, is easy to perform and with experience more than 25 examinations can be done in 1 hour.

5. *Permanency.* The records obtained are stable, not affected by humidity and can be used as part of a clinical record such as a roentgenogram or an electrocardiogram.

Method. The method now described depends upon the interaction of a chemically treated paper with sweat containing a reacting salt.

(a) *Preparation of Paper.* A 5% solution of tannic acid is prepared in distilled water, filtered and poured in a flat-bottom glass dish. Ordinary mimeograph paper is used and is allowed to soak in this solution for approximately 3 minutes. Metal containers are avoided. The paper is then dried and cut to desired dimensions. Where tannic acid is not available, a 5% solution of potassium ferrocyanide is used. The latter solution has the disadvantage of being less stable.

(b) *Preparation of the Salt.* Ordinary U.S.P. tincture of ferric chloride is diluted 1 part with 3 parts of alcohol, thus making a 25% solution. This preparation is stored in a well-stoppered, light-proof bottle.

(c) *Technique of Application.* The part to be tested is first thoroughly dried with an ordinary hair blower or an electric fan. A liberal amount of the prepared solution of ferric chloride is then evenly applied to the area with an ordinary cotton-tipped wooden applicator. The area is then dried thoroughly, and immediately thereafter contact is made between the chemically treated paper and the part to be tested. Contact is maintained for exactly 3 minutes. The procedure is explained to the patient before the test and it is advisable to have the patient in a comfortable position. For the study of palmar sweating the patient is seated beside a table with the forearm resting completely and evenly on its top.

(d) *Chemical Reaction.* The arrangement of the active sweat glands is portrayed upon the chemically treated paper. Sweat is approximately 99% water, and will carry with it in solution the readily soluble ferric chloride. The size and intensity of the pattern is directly proportional to the amount of sweat excreted. In the tannic acid technique the tannic acid reacts with iron to form a stain on the paper ranging between grey-blue and blue-black. The combination of tannic acid and iron salts is used commercially in the preparation of writing inks. When potassium ferrocyanide is used, the interaction with ferric chloride leaves a blue stain. This is the familiar Prussian blue reaction.

(e) *Interpretation of Results.* Using the tannic acid technique, the prints obtained on the paper fall into 4 categories: (0) or faint response; (1) or moderate response; (2) or strong response; and (3) or intense response. A (0) or faint response is characterized by fine, pin-point scattered dots, faintly grey in color. A (1) or moderate response is characterized by thicker dots and darker in shade. These dots are more numerous and begin to take on a linear pattern. A (2) or strong response is characterized by black speckles arranged in different sizes and occasionally appear confluent. A (3) or intense response shows diffuse blackening with thick blotches. In the potassium ferrocyanide

technique the results are analogous except that the end-points are blue. Examples of the prints using the tannic acid technique are shown (Fig. 1).

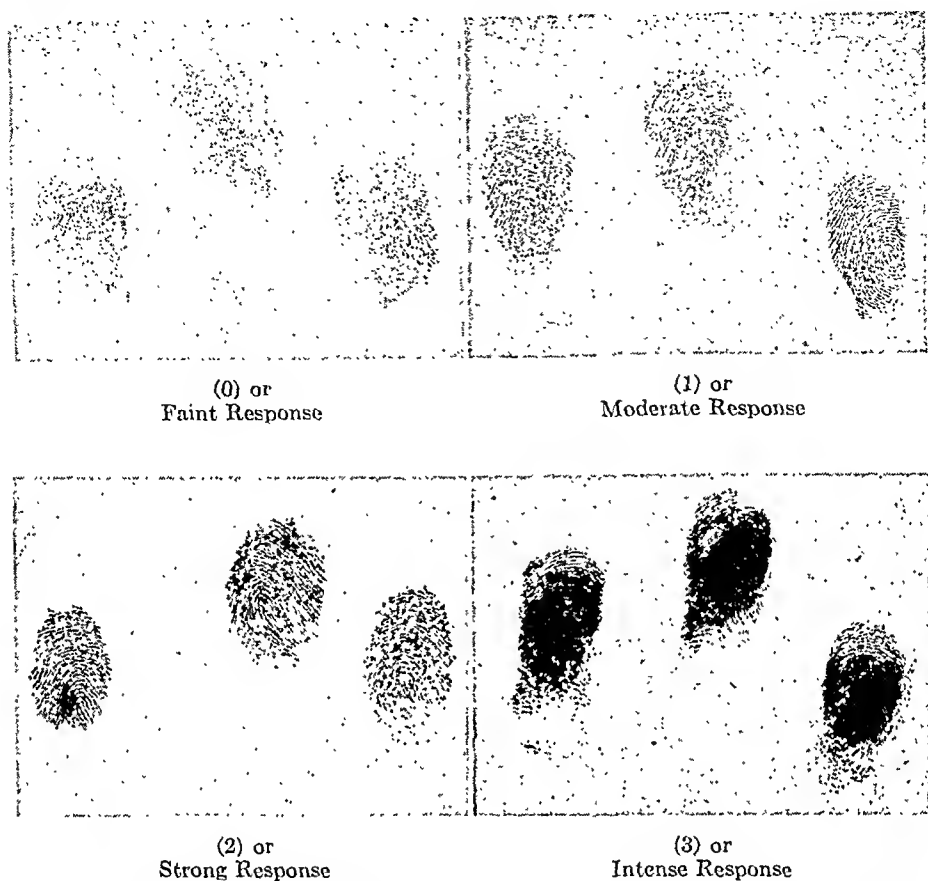


FIG. 1.—Classification of the sweat response as seen in the palmar aspect of the fingers.

PART II. THE SIGNIFICANCE OF PALMAR SWEATING

Sweating of the body occurs under diverse conditions. Its thermoregulatory function is well known. That temperature control of the body is not the sole function of sweating has now been well established. For the purpose of classification, sweating may be conveniently divided into the following headings, recognizing that they include mechanisms, localities and etiologic concepts.

1. *Thermo-regulatory.* This type is most important in that it controls body temperature. It is partly because of this function that man is able to inhabit the various zones of the world. It has been shown¹⁵ that in this type of sweating the sweat glands over the entire body surface except those of the palms and soles take part.

2. *Excretory.* Qualitatively sweat is similar to urine but only under unusual pathologic conditions, such as in uremia, will any significant urinary component be excreted. During exercise, however, there is an increase of lactic acid in sweat. Sweat contains approximately 99% water and is, therefore, the most dilute of animal fluids. Its most

important solid constituent is sodium chloride, and during excessive sweating hypochloremia may result. Water-soluble vitamins are also found in sweat.

3. *Drugs.* Coal tar products produce sweating; their action is central. Autonomic stimulating drugs such as acetylcholine and pilocarpine produce sweating by a peripheral action. The pharmacologic mechanism in sweating will be discussed below.

4. *Axillary.* The sweat glands in the axilla are fully developed at puberty and actively secrete under both emotional and thermal stimuli. According to Kuno¹⁵ the discharge of sweat from the axilla carries with it a characteristic scent which is considered to be of sexual significance.

5. *Gustatory.* Ingestion of spicy foods evokes sweat on the face, and is an example of a cranial parasympathetic response. The significance of this type of sweating is not clear.

6. *Spinal Reflex.* This type of sweating occurs in the transverse syndrome of the spinal cord, and is seen only in pathologic conditions.

7. *Emotional.* Emotional, intellectual and sensory stimuli will cause a type of sweating involving palms, soles and axillæ. This type of sweating is the main topic of this paper and is seen in both physiologic and disturbed states.

Normally emotional sweating is commonly seen in states of anticipation and has sometimes been referred to as anticipatory sweating. A student before an examination, an expectant father before the delivery of his child, or a draftee waiting for his number will show sweating, particularly of the palms. The relationship of emotions to sweating was noted by Sanctorius¹⁹ in 1614, when the first scientific studies on perspiration were performed. Sanctorius shrewdly observed: "a body which is at rest whilst the mind is violently agitated has a stronger perspiration and less weight than a body that is strongly moved whilst the mind is at rest." Interestingly, Hermann and Luchsinger¹⁰ in 1878 referred to the profuse sweating of the foot pads of cats as "Angstschweiss." The relationship of palmar sweating to emotional stress or strain has expression in many fields of human endeavor. A baseball player will moisten the palm of his glove or hand with saliva in anticipation of a play. A woodman performs a similar act when he is about to grip his axe. As Kuno¹⁵ points out, moistening the palms is a physiologic property and does not have an ethnologic distribution. The expression "spitting on the palm" is found in many languages, and in the Chinese and Japanese languages the expression conveys a meaning of physical and mental stress.

The relationship of sweating to mental and emotional stimuli indicates a cortical control. Bechterew¹ in 1905 demonstrated that stimulation of a localized area of the cortex evoked sweating. Bieber and Fulton² indicated that this area (area 6 of Brodman) was also important in the grasp reflex. Kennard, Viets and Fulton¹³ showed on clinical grounds that pathologic lesions in this area produced impairment of skilled movements, forced grasping, vasomotor changes and sweating. Rabiner¹⁷ found that patients with so-called autonomic imbalance without any demonstrable organic disorder showed reflex grasping

when in a state of panic. That the cortex is not the only pathway in sweating is suggested by the work of Wang, Pan and Lu.²² These investigators demonstrated that following section of the brain above the level of the hypothalamus, a sweat response could be obtained by faradic stimulation of afferent nerves. The relationship between sweating and parasympathetic centers in the diencephalon was noted by Cushing,⁴ who observed profuse sweats, vomiting and vasomotor changes after injections of pilocarpine and pituitrin in the region of the interbrain. Cushing looked upon the interbrain as a "station for vegetative impulses easily affected by psychic impulses," and suggested that conditions might conceivably arise whereby hormones discharged in sufficient strength would call forth a parasympathetic response.

On anatomic grounds it has been established that the sweat fibers originate from the cells of the lateral horn of the spinal column and travel along the sympathetic trunk. Extirpation of the sympathetic fibers supplying the lower extremity causes anhidrosis of most of the lower extremity. These sweat fibers along with the other sympathetic components are contained in the peripheral nerves. Stimulation of the sciatic nerve of the cat, for example, will produce sweating of the foot pads. Severing a peripheral nerve will leave its innervated part anhydrotic.

Although sweating on anatomic grounds travels along a sympathetic pathway, pharmacologically it behaves as a parasympathetic mechanism. Pilocarpine, physostigmine, and acetylcholine will stimulate sweating; atropine will inhibit it. Epinephrine, a powerful sympathetic stimulator, does not cause sweating in man. Ergotoxin, which is a sympathetic inhibitor, has practically no affect on sweating. Dale and Feldberg⁶ showed that a sympathetic nerve may carry postganglionic fibers which are cholinergic. They obtained from the venous effluent of the hind foot of a cat, after sciatic stimulation, an acetylcholine-like substance.

That sweating, a parasympathetic response, occurs in states of increased sympathetic activity may at first seem confusing. "Breaking out in a cold sweat" is a common expression. This confusion may result from the arbitrary separation of the autonomic system into the parasympathetic and sympathetic divisions. This separation implies a reciprocity of action. According to Cannon³ during emotional crises, such as in fright and rage, the sympathetic system tends to discharge *en masse*. It does not mean, however, that the parasympathetic system is inactive or inhibited. Gellhorn⁸ has recently shown that emotional excitement evokes a stimulation of *both* branches of the autonomic nervous system, although under normal conditions the sympathetic system predominates. The principle of reciprocal innervation of both divisions of the autonomic nervous system is also not borne out on clinical grounds. It is practically impossible to find a pure example of vagotonia or sympathotonia. Thus a vagotonic individual may have a slow pulse but wide pupils. In hyperthyroidism there may be a rapid pulse, exophthalmus, and hyperglycemia; yet these patients often complain of diarrhea and moist palms.

It has not been sufficiently well appreciated that sweating of the palms differs from sweating on the general body surface. Anatomically, there are more sweat glands per square area in the palm than anywhere else in the body. Krause¹⁴ found twice as many sweat glands per square

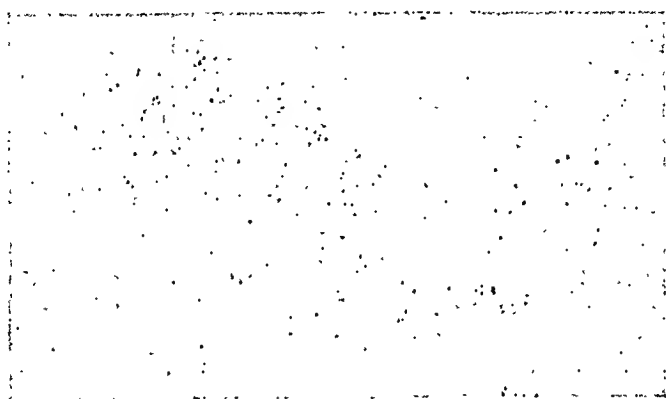


FIG. 2.—Sweat response of the dorsum of the hand in a patient with neuro-circulatory asthenia. Compare with Fig. 4.

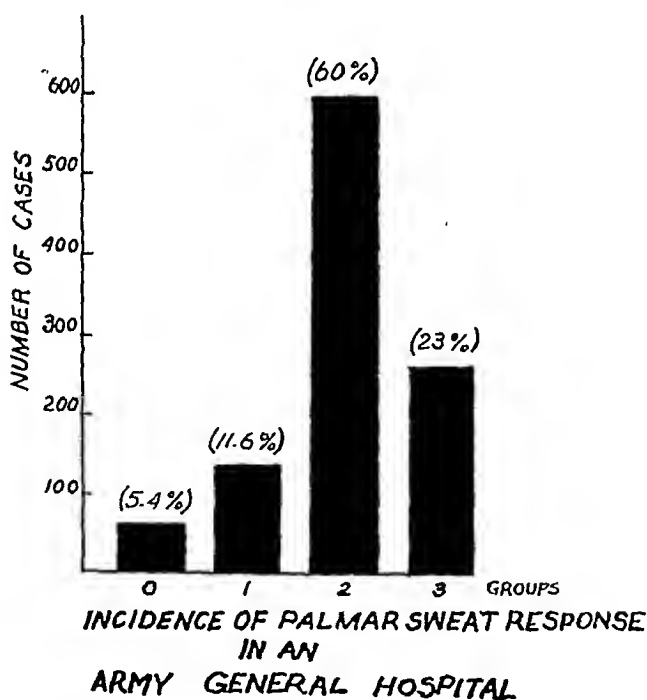


FIG. 3.

area on the palm as on the dorsal aspect of the hand, 4 times as many as on the chest, and over 5 times as many as on the back and buttock. The sweat glands on the palm are arranged in linear fashion on ridges. These ridges assume a characteristic pattern and are arranged in such

a way as to assure maximum grasping and tactile facility.¹¹ Functionally, the amount of perspiration on the palm is from 5 to 10 times as great as that of the general body surface.¹⁵ Studied microscopically¹² the secretion of sweat on the palm and sole takes place continuously, whereas it is intermittent on the general body surface. Moreover, palmar sweating differs from that of the general body surface in that under ordinary conditions it is not influenced by outside temperatures.¹⁵

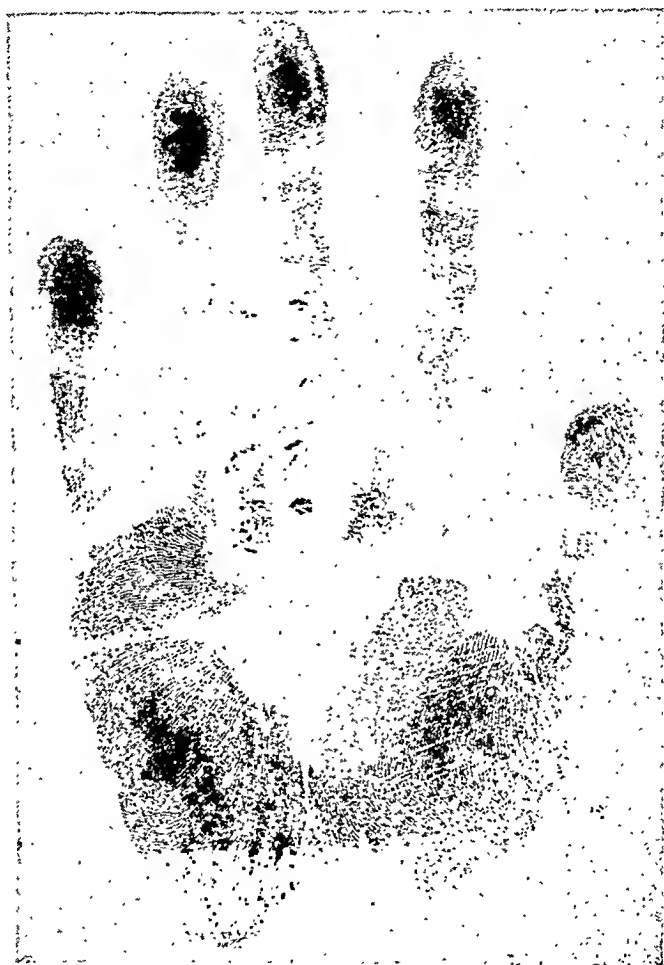


FIG. 4.—An example of excessive palmar sweating seen in a patient with neuro-circulatory asthenia.

Exposure of the body to a high temperature does not augment sweating of the palms. Experimentally it can be demonstrated that palmar sweating may be evoked by mental stimuli.¹⁵ For instance, problems in simple arithmetic will cause a distinct and measurable increase in sweat confined to the palms and soles. In a relaxed state, such as in sleep, the palms are characteristically dry. Finally, the palm is one of the few places where emotional sweating takes place, and is peculiarly an indicator of emotional disturbances. In anxiety neurosis, where

autonomic phenomena are frequent, excessive sweating of the palms is seen²¹ (Figs. 2 and 4).

By utilizing the galvanic skin reflex, palmar sweating has been studied extensively. A complete review of the subject has been given by Darrow.⁷ However, the galvanic skin reflex study requires a complicated apparatus. Also, the apparatus used is not generally available to physicians, and is subject to technical errors.

To overcome these objections a colorimetric technique using impregnated paper was devised. A study of the palmar sweat response was made in over 1100 patients in an Army General Hospital²⁰ (Fig. 3). It was observed that a high percentage of these patients showed manifestations of a disturbed autonomic nervous system, one of the striking features of which was excessive palmar sweating. Approximately 25% of the patients showed a (3) response, and over 80% showed a combined (2) and (3) response. Invariably, in those patients who showed a (3) or intense response, evidence of emotional strain or a disturbance of the autonomic nervous system was present. These patients made poor soldiers and were hospitalized frequently. It is anticipated in the near future to study palmar sweating in well seasoned troops.

The clinical observation of excessive palmar sweating is not new. DaCosta⁵ in 1871 in his classical paper on the "irritable heart" stated: "But there was also evidence of disorder of the sympathetic nervous system as shown in the itching of the skin and excessive perspiration from which many suffered. Inordinate sweating of the hand was several times complained of (as in case 159)." It is interesting to note that DaCosta advised the use of atropine which has later been shown to be a powerful antiparasymphathetic drug. In an analysis of 200 cases of DaCosta syndrome, Wood²³ in 1941 found visible sweat on the palms in 67% of the patients. It is now generally agreed that in this disorder there are emotional disturbances as well as disturbances of the vegetative nervous system. Palmar sweating is merely one expression of these changes. Palmar sweating is such a constant and striking feature of neuro-circulatory asthenia that its presence should always be looked for as a point in diagnosis (Fig. 4).

Summary. 1. A test for the palmar sweat response has been devised which has several advantages over other methods previously used.

2. Various kinds of sweating are discussed.

3. The palmar sweat response was observed in more than 1100 patients and the clinical significance discussed.

4. Palmar sweating is unique and differs from general body sweating on anatomic and physiologic grounds. It attains special significance when it is looked upon as a cholinergic phenomenon related particularly to emotional activities.

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THE VALUE AND LIMITATIONS OF THE CONGO RED TEST FOR AMYLOIDOSIS

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For the past 11½ years the Congo red test has been used at our institution as a diagnostic aid in determining the presence of generalized amyloidosis. During this time the technique introduced by Bennhold² has been twice modified, first by Friedman and Auerbach,³ and later by Taran.⁶ The method used by the latter author has been adopted by the committee of Standard Laboratory Procedure of the American Trudeau Society.¹

In this period there were 468 persons who at autopsy revealed varying degrees of amyloidosis. The etiologic factor in the production of amyloidosis was chronic pulmonary tuberculosis in all but 7 cases. Of the latter, 5 had lung abscesses, 1 bronchiectasis and 1 syphilis. Two hundred and forty-six of these had Congo red tests performed before death. With this opportunity to compare the results of the Congo red test with the findings at autopsy, evidence was accumulated to evaluate the test, to attempt to find the cause for false results, to study the effect of repeated Congo red tests in the same patient, and to determine if excretion of the dye in the urine is of aid in the diagnosis of the amyloid nephrotic syndrome.

Material. This study is based upon 446 autopsy cases in which Congo red tests were performed during life. Two hundred and forty-six revealed amy-

loidosis of varying degrees at autopsy; the remaining 200 were consecutive cases in which no amyloidosis was found in any of the organs.

There were 416 Congo red tests done on the 246 patients with amyloidosis (1.7 tests per patient); while there were 233 tests performed on the 200 patients without amyloidosis (1.2 tests per patient). The higher percentage of tests performed in the former group is explained by two factors: (1) when the Congo red test resulted in a 100% absorption, as was the case in most individuals with amyloidosis, it provoked repetition of the test for verification; (2) the persons with amyloidosis in general had a longer duration of the pulmonary disease and, therefore, there was greater opportunity to repeat the test.

We⁵ have previously established the standard that 90 or 100% absorption of the Congo red dye is to be considered a positive result. Harmon and Kernwein⁴ prefer to make a diagnosis of amyloidosis only when the dye is completely removed from the blood after an hour (100%).

Comparison of Congo Red Test and Autopsy Findings Showing Amyloidosis. In Table 1 (A) the figures representing the percentage of Congo red absorption are based on the last test done during life, except for the 100% determinations. In the latter the first 100% determination is recorded.

In those cases with insufficient dye in the first specimen, the result is recorded as 100% absorption (14 cases). All of these patients at autopsy showed marked amyloidosis in at least 1 organ, and in 12 the liver parenchyma was almost completely replaced by amyloid. Therefore, the insufficient dye in the first specimen was probably not due to any "errors," discussed below, but rather due to the rapid absorption of the dye by parenchymal amyloid before the first (standard) specimen of blood was procured. The fact that most patients with marked amyloidosis at autopsy showed Congo red tests of insufficient dye alternating with 100% absorption on subsequent examinations supports this contention.

In 25 of 103 cases (24.3%) in which the test was performed 2 months or less before death, there was less than 90% absorption of the dye. This represents a false negative result.

In 86 of the entire group of 246 cases there was less than 90% absorption, a false negative diagnosis of 30.9%. Since, however, in many the amyloid was probably deposited after the test was performed, all the false negative results cannot be attributed to defects in the test.

Comparison of Congo Red Test and Autopsy Findings Showing no Amyloidosis. In Table 1 (B) the figures representing the percentage of Congo red absorption are based on the last test done during life. In all instances the test was performed 6 months or less before death. In those cases with insufficient dye in the first specimen, the test is recorded as 100% absorption (8 cases). The insufficient dye was probably due to one or more of the technical "errors" listed below, since repetition of the test, unlike the repetition in the amyloid group, failed to reveal 100% absorption.

Five of 119 cases in which the Congo red test was done 2 months or less before death showed 90 to 100% absorption, a false positive result of 4.2%. Thirteen of 200 cases in which the Congo red test was performed 6 months or less before death showed 90 to 100% absorption, a false positive result of 6.5%.

It is possible that a 100% absorption reported 5 to 6 months before death may represent small amounts of amyloid that resorbed prior to death. We do not have sufficient data to confirm this point.

TABLE 1.—PER CENT ABSORPTION OF CONGO RED IN AMYLOID AND NON-AMYLOID CASES

A. <i>Amyloid</i>										
Interval before death	39% or less	40 to 49%	50 to 59%	60 to 69%	70 to 79%	80 to 89%	90 to 99%	100%	Total	
2 wks. or less	1	0	1	3	0	0	2	23	30	
3-4 wks.	1	1	3	3	2	2	3	17	32	
5-8 wks.	0	1	1	4	1	1	5	28	41	
2½-4 mos.	5	4	6	2	0	0	1	19	37	
5-6 mos.	3	4	1	0	3	1	5	9	26	
7-12 mos.	3	5	5	2	0	0	0	18	33	
12 mos.-2 yrs.	3	2	2	2	1	1	1	14	26	
Over 2 yrs.	0	0	2	2	1	1	1	14	21	
B. <i>Non-amyloid</i>										
2 wks. or less	7	4	10	6	8	2	1	3	41	
3-4 wks.	12	1	12	4	4	2	0	0	35	
5-8 wks.	13	3	11	7	7	1	0	1	43	
2½-4 mos.	9	8	14	8	6	3	0	2	50	
5-6 mos.	10	1	4	7	2	1	3	3	31	

TABLE 2.—CHANGES IN PER CENT ABSORPTION IN REPEATED TESTS

Interval between tests	No change			Less absorptions				Greater absorption			
	100%	90 to 99%	Below 90%	90% to below	10 to 90%	100 to below 90%	Below 90%	Below 90 to 90%	90 to 100%	Below 90 to 100%	Below 90%
4 wks. or less	6	1	0	0	0	1	0	0	1	1	0
6 wks.	4	0	0	0	0	0	1	0	0	0	0
8-10 wks.	3	0	1	1	0	0	0	0	1	2	1
12 wks.	3	0	1	0	0	0	0	1	1	0	0
4 mos.	4	0	2	1	1	0	0	0	0	1	0
5 mos.	8	0	0	0	1	0	0	1	0	0	1
6 mos.	3	0	0	0	0	0	1	0	1	4	2

Sources of Error. The results of the Congo red test (Table 1) show that there are many more false negative than false positive reports. The possible sources of error may be either technical or physiologic. In general the technical errors are dependent upon whether or not the first (standard) specimen is too light or too dark. If too dark, the test may be falsely negative, when there are only small amounts of amyloid in the tissues. In this case, there is not sufficient absorption of dye to alter appreciably the highly concentrated standard. If the first specimen is too light the test may be either wrongly negative or positive, usually the latter.

The first specimen may be too dark, if the patient is markedly undersized (children and emaciated adults) (Taran and Eckstein⁷), or if the same syringe is used for securing the first specimen as was used to inject the dye. The first specimen may be too light, if the patient is markedly oversized; if the dye is injected partially into the tissues or varying amounts are left in the syringe; or if the first specimen is taken longer than 4 minutes after the injection of the dye.

In those cases in which the technical errors have been eliminated, physiologic factors may explain the erroneous results. The test is not sufficiently delicate to detect minimal amounts of amyloid. In none of our cases did we obtain a positive result where there were small

amounts in the spleen alone with or without involvement of the blood-vessels of the liver; and in only a few cases where there were moderate amounts in the spleen. This constituted the source of error in 75% of our false negative results. If the dye is excreted unduly rapidly into the urine before the second specimen is procured, there may be a false impression of absorption.

If the amyloid is absorbed during the interval between 2 tests there may be an apparent erroneous report. In our series there were 7 cases in which this might have been a possibility. Since, however, at necropsy we found no evidence that amyloid was or ever had been present in the tissues, we have listed this as a false positive result.

Repetition of the Congo Red Test. It has been assumed previously that a Congo red test, repeated soon after the first, was valueless, since the amyloid in the tissues having already taken up the dye from the first test would not be prepared to absorb that from the second, unless additional new amyloid were laid down during the interval period. It has been more or less arbitrarily stated that there should be an interval of at least 3 months between tests. There were 24 repeat tests done at intervals of less than 3 months (Table 2). In 21 of these the absorption remained at the same level or showed increased absorption. There were 15 repeat tests at intervals of 6 weeks or less, in 13 of which the absorption was unchanged or increased. There were 10 tests repeated within 4 weeks, of which 9 tests were unchanged or increased.

The 3 cases in the entire group of 24 which showed diminished absorption when the test was repeated in less than 3 months were as follows: (1) A test which showed 100% absorption originally dropped to 75% when the test was repeated after 4 days. It returned again to 100% after a 10 month interval. (2) A test repeated in 6 weeks showed a drop from 55% to 40%. When the test was repeated 8½ months later it revealed a 95% absorption. (3) The test repeated after 2½ months showed a drop from 90 to 60%. Since death occurred 2 years after the last test, amyloid may not have been present when either of the tests was performed.

In the group of non-amyloids with 20 repeat tests, a false positive result was never found twice on the same patient, with 1 exception. This person had 4 tests at about monthly intervals as follows: 100%, 50%, 100%, 10%.

Although the series of 44 cases is small, it may be concluded that the Congo red test can be repeated in 4 weeks or more, and reasonably safely in 2 weeks. Repeated tests will weed out the false positives, since in a true amyloid once 100% absorption always 100%. In the non-amyloids this is unlikely.

Excretion of Amyloid in the Urine. The urine was tested for the excretion of Congo red within 1 hour after injection in about 75% of all the cases. Normally the dye is ultimately excreted in the urine, but it is only in the presence of renal tubular damage that it is excreted within the first hour (Harmon and Kernwein⁴). In only 1 non-amy-

loid case was there such excretion, the absorption being 45%. This patient had a nephrotic syndrome, which was not, however, on an amyloid basis.

In 13 of the amyloid cases there was an excretion in the urine. In 1 of these, 2 of 6 tests showed excretion of the dye. In 5 of the 13, the second or third tests failed to reveal excretion. In 11 cases there was evidence of renal damage with large amounts of albumin, casts, red blood cells and white blood cells in the urine and slight to marked edema present at the time the test was performed. In all but 2 instances the test revealed 100% absorption, not only on this but on subsequent or previous tests.

At autopsy it was found that 5 cases died of uremia and 6 of progressive pulmonary tuberculosis with clinical and pathologic signs of pre-uremia. In 77 cases, in addition to these 11, there were well-marked nephrotic syndromes, and the patients ultimately succumbed in uremia and pre-uremia. In none of these was there excretion of the dye.

In 2 cases there was no evidence of renal disturbance, either clinically or pathologically, either at the time that the test was done or at autopsy 10 or 14 months later. The tests both showed 50% absorption.

Therefore, while the dye may be excreted in nephrotic syndromes, it is apparently adequately withheld by the kidney when the nephrosis is on an amyloid basis. A low renal threshold for that particular substance may be the explanation why, without any renal pathology, the dye is excreted.

Conclusions. The results of 649 Congo red tests for amyloidosis performed on 446 patients have been reviewed in order to evaluate the test and to determine the sources of error. It has proved to be a valuable procedure, in spite of a certain proportion of erroneous results, which in our series has been calculated as 24.3% false negatives and 4.2% false positives.

The sources of error have been enumerated. The presence of only minimal amounts of amyloid is the principal reason for false negative results, while technical errors are probably the chief cause of false positive reports. The latter may be eliminated by repetition of the test at an appropriate interval, which we have shown should be 1 month or more.

The determination of the presence of Congo red in the urine within 1 hour after injection of the dye has been of little value in the diagnosis of amyloid nephrosis.

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CREATINURIA IN HYPERTHYROIDISM AND IN ESSENTIAL HYPERTENSION

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THE increase of urinary creatine in many cases of exophthalmic goiter was first reported by Shaffer¹¹ in 1907. He found it in 8 of 12 cases studied. In 1931 Kepler and Boothby⁶ summarized the literature to that time on creatinuria in hyperthyroidism and reported that in exophthalmic goiter the incidence of creatinuria was 61%, in adenomatous goiter with hyperthyroidism 63%, while in their control groups it was only 9% among males and 23% among females. They concluded that creatinuria could be considered a "fairly common and characteristic phenomenon of hyperthyroidism." Palmer⁸ showed that in those cases of hyperthyroidism in which the creatine content of the urine was increased definitely, the creatinuria decreased after the administration of iodine. Richardson and Shorr,^{9,10} who have felt, contrary to the conclusions of many other workers, that urinary excretion of creatine could be used as a clinical sign of value in hyperthyroidism, recommended a creatine tolerance test in addition to determinations of spontaneous excretion of creatine as giving a still more accurate method of indicating the correlation with hyperthyroidism. Thorn,¹³ using Richardson and Shorr's method of performing the creatine tolerance test, with a slight modification, reported a high degree of correlation between the results of this test and hyperthyroidism; but Sohval, King and Reiner,¹² using Richardson and Shorr's method, reported findings which did not confirm these results. They, therefore, doubted the clinical value of the test. In 1939 Wang¹⁵ reviewed completely the subject of creatine metabolism and reported additional clinical and experimental investigations. Wang concluded that in hyperthyroidism the urinary excretion of creatine usually is increased, but that this is not definite nor specific enough to be of value clinically.

Two facts are generally recognized: (1) that most normal adults, especially men, do not excrete significant amounts of creatine in their urine, and (2) that increased creatinuria occurs in several conditions other than hyperthyroidism such as the muscular dystrophies, acute anterior poliomyelitis, febrile states, the postpartum state, and so forth.

Recently, Tierney and Peters,¹⁴ using a new sensitive method employing the photo-electric colorimeter, correlated the levels of creatine

in the blood serum with those in the urine of normal adults and of hyperthyroid patients. They found that creatine acted like a threshold substance, appearing in the urine whenever the blood level exceeded 0.58 mg. per 100 cc. They also performed creatine tolerance tests and determined that, after the ingestion of creatine, the usually high serum creatine and the creatinuria of the patient who had hyperthyroidism were increased more proportionately than those of the normal adult.

That an increase in the basal metabolic rate occurs in many cases of essential hypertension has been observed by many workers in the past 20 years. Furthermore, in spite of the increased metabolism and some rather marked resemblance of symptoms at times to hyperthyroidism, many of these patients have been demonstrated not to have hyperthyroidism.

Mountain, Allen and Haines⁷ analyzed 827 cases of essential hypertension from the Mayo Clinic from the standpoint of the basal metabolism and thyroid status. They reported a basal metabolic rate greater than +15% in 7% of the cases of hypertension in Groups 1 and 2, in 12% of the cases of hypertension in Group 3, and in 27% of cases in Group 4.* They felt that the elevated basal metabolic rate, found in many cases of hypertension was not dependent on a disturbance in thyroid function.

From the standpoint of circulatory dynamics, Weiss¹⁶ has pointed out that the pulse rate, velocity and amount of blood flow are not increased in proportion to the metabolism in cases of arterial hypertension and increased metabolism, in contrast to the picture in the usual case of hyperthyroidism.

Crile and McCullagh³ reported on levels of iodine in the blood in cases of essential hypertension and increased metabolism without hyperthyroidism. Levels of iodine in the blood in 11 such cases were normal in 5, slightly elevated in 3, and abnormally high in 3. Curtis,⁴ however, showed that in hypertension, even without an elevated basal metabolic rate, there was not infrequently an inexplicable increase of iodine in the blood. Crile and McCullagh felt that a low level of iodine in the blood was nevertheless of value in ruling out hyperthyroidism.

Practically no determinations of urinary creatine have been reported in the literature to date on this specific group of patients who have hypertension and an elevated metabolic rate but without hyperthyroidism. Wang¹⁵ analyzed 7 cases of hypertension, without regard to the basal metabolic rates, and found normal elimination of creatine in 6 cases and somewhat high elimination in 1 case. Sohval, King and Reiner¹² reported no creatinuria in 6 cases of hypertension, and in 4 of these the basal metabolic rate was +15% or more.

* At the clinic, cases of hypertension are divided into 4 groups, depending on the severity of the disease.⁵ The severity of the hypertension is estimated to a large extent by the pathologic changes which can be seen in the ocular fundi. In hypertension Group 1, the changes in the retinal arterioles are minimal. In Group 2, the arteriolar changes are definite, but retinitis is not present. In Group 3, there are angiospastic changes, retinitis and pronounced sclerotic changes in the arterioles. Group 4 is characterized by edema of the optic disk in addition to the changes that are present in Group 3.

The present study was undertaken with a double purpose in mind: (1) to reëvaluate creatinuria as a sign of hyperthyroidism especially as it may help in ruling in or out hyperthyroidism in cases of hypertension with elevated basal metabolic rates, and (2) to ascertain if any difference occurs in these 2 groups of cases, which, even if not helpful in clinical differentiation, might serve as supportive evidence to that already accumulated that the elevated basal metabolic rate in some cases of hypertension is on a different basis from that in hyperthyroidism.

TABLE 1.—COMPARISON OF RESULTS

		Excretion of creatine in 24 hours					
		Less than 90 mg.		90 to 135 mg.		More than 135 mg.	
	Patients	Patients	%	Patients	%	Patients	%
Exophthalmic goiter	29	4	14	5	17	20	69
Males	17	4	..	3	..	10	..
Females	12	2	..	10	..
Adenomatous goiter with hyperthyroidism	10	2	20	2	20	6	60
Males	4	1	..	2	..	1	..
Females	6	1	5	..
Adenomatous goiter without hyperthyroidism	6	5	83	0	..	1	17
Females	6	5	1	..
Hypertension (B.M.R. +15 per cent or more)*	18	12	66	3	17	3	17
Males	10	9	1	..
Females	8	3	..	3	..	2	..
Hypertension (B.M.R. less than +15 per cent)	17	11	65	5	29	1	6
Males	11	7	..	4
Females	6	4	..	1	..	1	..
Total cases of hypertension	35	..	66	..	23	..	11
Total cases of hyperthyroid- ism	39	..	15	..	18	..	67

* Clinically not hyperthyroidism.

Material and Methods. In order to make the test as simple and practical as possible, no special dietary restrictions were imposed. In this respect our data may be compared to those of Wang,¹⁵ and Brøchner-Mortensen and Møller,^{1,2} whose patients were allowed to receive the regular hospital diet. Samples of urine for 12 or 24 hours were collected as accurately as possible. In many instances 2 or 3 successive 24-hour specimens were obtained. Creatine was determined according to the method of Folin, after conversion to creatinine by boiling with picric acid solution. The values are calculated on the basis of the total output of creatine in 24 hours and are expressed in milligrams.

Our cases included 29 cases of exophthalmic goiter before any compound solution of iodine (Lugol's solution) had been given, 10 cases of adenomatous goiter with hyperthyroidism, 6 cases of adenomatous goiter without hyperthyroidism and 35 cases of essential hypertension, in 18 of which the basal metabolic rate was elevated to +15% or more.

The ages of the patients varied as follows: from 17 to 59 years for those having exophthalmic goiters; from 23 to 64 years for those having adenomatous goiter with or without hyperthyroidism, and from 25 to 63 years for those having hypertension.

In all but 5 of our 29 patients who had exophthalmic goiter, subtotal thyroidectomy was performed at the clinic, and the removed thyroid tissue showed on histologic study the confirmatory findings of diffuse parenchymatous hypertrophy.

The cases were grouped according to whether the creatine excreted in the urine was less than 90 mg. in 24 hours, 90 to 135 mg. in 24 hours, or more than 135 mg. in 24 hours.

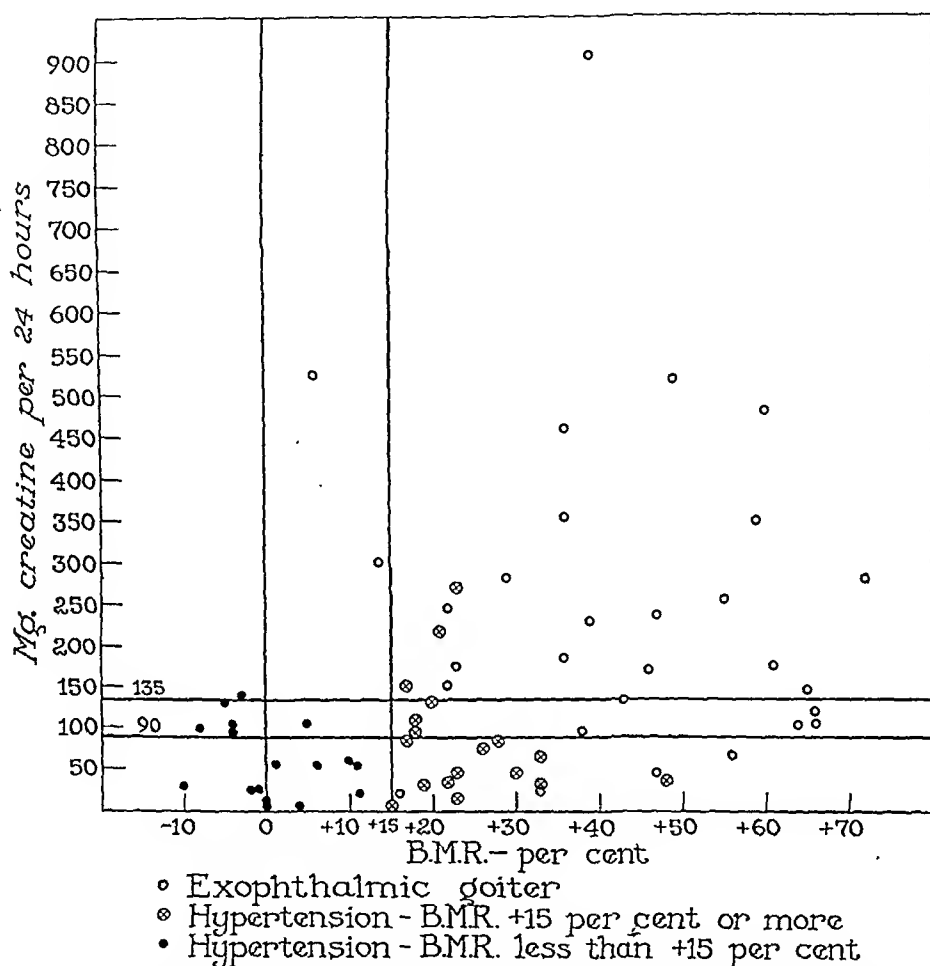


FIG. 1.—Comparison of basal metabolic rates and urinary excretion of creatine in cases of exophthalmic goiter and hypertension. Of the 3 patients having hypertension and basal metabolic rates greater than +15% and more than 135 mg. of creatine in the urine, 2 were women, aged 46 and 48 years, and 1 was a man, aged 36 years.

Results. Of the 29 patients who had exophthalmic goiter, 20 (69%) excreted more than 135 mg. of creatine in 24 hours, 5 (17%) excreted 90 to 135 mg. and 4 (14%) excreted less than 90 mg. Of 10 patients with adenomatous goiter with hyperthyroidism, 6 (60%) excreted more than 135 mg. of creatine in 24 hours, 2 (20%) excreted from 90 to 135 mg. and 2 (20%) excreted less than 90 mg. (Table 1). The sex distribution of the patients has been indicated in Table 1. It is

seen that the totals were fairly evenly divided between the sexes, but that the differences in the results by sex were not large enough for any definite conclusions to be drawn on this basis.

Of 18 hypertensive patients whose basal metabolic rates were $+15\%$ or more, 12 (66%) excreted less than 90 mg. of creatine per 24 hours, 3 (17%) excreted from 90 to 135 mg. and 3 (17%) excreted more than 135 mg. Similarly, of 17 hypertensive patients whose basal metabolic rates were less than $+15\%$, 11 (65%) excreted less than 90 mg. of creatine per 24 hours, 5 (29%) excreted between 90 and 135 mg. and 1 (6%) excreted more than 135 mg. (Table 1). In these 2 groups of hypertensive patients, the excretion of creatine is obviously similar, regardless of elevation of the basal metabolic rate. It might be pointed out further that, in the cases of hypertension in general, the results did not differ much from those which would be expected in a random group of normal adults of both sexes without hypertension. In Table 1, also, the percentage of cases of hyperthyroidism and of hypertension in each range of excretion of creatine are presented together for ready comparison. It is seen that, in the majority of cases of hyperthyroidism, whether it was associated with exophthalmic goiter or adenomatous goiter, more than 135 mg. of creatine was excreted in 24 hours; whereas in the majority of cases of hypertension, either with or without an elevation of the basal metabolic rate, less than 90 mg. of creatine was excreted in 24 hours. These findings are illustrated in Figure 1 which shows that although, in general, patients who have exophthalmic goiter excrete more creatine than the hypertensive patients with or without an elevated basal metabolic rate, there is no direct proportionality between the creatine content of the urine and the basal metabolic rate, even in the hyperthyroid patients considered alone.* The wide scattering of the results, as seen on the graph, limits markedly the value of spontaneous creatinuria as a clinical sign in these conditions, but these figures certainly are consistent with the opinion that the elevated basal metabolism in essential hypertension rests on a different physiologic basis than that in hyperthyroidism.

Summary. Values for urinary creatine have been determined in cases of hyperthyroidism and in cases of essential hypertension with or without an elevated basal metabolic rate. Under the conditions of our study the majority of patients who had hyperthyroidism excreted more than 135 mg. of creatine in 24 hours, whereas the majority of patients who had essential hypertension even with an elevated basal metabolism excreted less than 90 mg. of creatine in 24 hours.

Conclusions. 1. The wide scattering of the results limited markedly the value of spontaneous creatinuria as a clinical sign for ruling hyperthyroidism in or out in cases of essential hypertension with elevated basal metabolism.

2. The results in general tended to substantiate the opinion that the elevated basal metabolism in essential hypertension rested on a different physiologic basis than that in hyperthyroidism.

* This point has been stressed by Kepler and Boothby⁶ and Brøchner-Mortensen and Møller,^{1,2} as well as others.

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THE EFFECT OF CALCIUM PANTOTHENATE AND PARAAMINOBENZOIC ACID ON GRAY HAIR IN MAN

A STUDY ON A GROUP OF YOUNG AND OLDER INDIVIDUALS

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REPORTS of the effect of calcium pantothenate and paraaminobenzoic acid* on the color of gray hair in man or animals, have been confusing as to which of the two drugs is the more important; whether both are necessary or, in the case of man, whether an unquestionable effect has ever been observed. In this paper an attempt is made to clarify this state of affairs by the addition of new data as well as by a brief discussion.

It has been reported^{10,11,16-19,21} that a deficiency of the filtrate factor of the vitamin B complex is accompanied by graying of fur in rats and dogs. The administration of the filtrate factors plus other vitamin B factors apparently helped to darken the fur in some animals.

Morgan, Cook, Davison and Simms^{10,19} first noted that the substance active in curing graying, is contained in the filtrate fraction of vitamin B₂ complex, *i. e.*, it is in the water extract of yeast, lime or rice bran after thiamin, pyridoxine and riboflavin have been removed. These investigators also found that supplying this filtrate fraction cured grayness of fur in animals. Ralli, Clarke and Kennedy,²⁵ found that

* Calcium pantothenate will be referred to as Ca.P., paraaminobenzoic acid as PABA, and pantothenic acid as P.A.

animals with low salt intake developed graying of fur much sooner than those on high salt intake.

In 1940, Gyorgy, Poling and Subbarrow⁹ observed that crude concentrates of P.A. had a definite curative effect on nutritional achromotrichia in rats. However, the fur did not become completely black in most instances, and depigmented areas often persisted. Williams³³ failed, however, to find any preventive or curative effect in gray hair in rats when P.A. was added. Frost, Moore and Dann⁷ reported that certain liver extracts containing P.A. cured or prevented nutritional achromotrichia in rats, while synthetic Ca.P. had a negligible effect.

Evidence that P.A. was not the only factor in the graying of hair began to appear.^{7,9,20,21} Martin, Wisinsky and Ansbacher¹⁵ stated that PABA modifies melanin and that Ca.P. has no influence.

Ansbacher¹ reported that PABA was a factor in the prevention of achromotrichia in the rat, and a growth promoting factor for the chick. By means of this vitamin, he was able to overcome apparent grayness of the hair of rats, while another group of rats not given this vitamin continued to show typical achromotrichia. Martin and Ansbacher^{13,14} confirmed the previous evidence that PABA has anti-gray hair activity in rats and mice. Unna, Richards and Sampson³² and Emerson⁴ found PABA ineffective for controlling achromotrichia in animals, but that P.A. and Ca.P. were beneficial in curing and preventing gray hair in laboratory animals.

Investigation of the effect of Ca.P. and PABA on human patients with gray hair followed these studies in animals. Punnett and Bader²³ gave 10 to 20 mg. of Ca.P. for from 1 to 6 months to 25 men and women, and in some cases supplemented this with the whole vitamin B complex. They obtained favorable results in a large proportion of cases. Sieve²⁷ reported beneficial effects after the administration of PABA to patients with definite achromotrichia. In 30 cases, PABA was given alone; in 20 cases, estrogenic hormones were administered at the same time. He observed marked darkening of hair within 2 months, and recommended 200 mg. of PABA daily as a reasonable therapeutic dose. Sieve and Ansbacher²⁹ reported the restoration of color of gray hair in more than 300 persons of both sexes after using 50 to 600 mg. of PABA a day. In a later paper²⁸ Sieve reported 800 cases with noticeable return of color to gray-haired individuals after treatment for 3 to 8 weeks. Since these results have been questioned,^{2,24} it was believed that the present studies should be reported.

Procedure. Three groups of patients were studied. The first group, 19 elderly (over 55 years of age) males and females with white or graying hair, was selected from the wards of the 3rd Medical Division of Goldwater Memorial Hospital, where they were confined with a chronic disease, such as rheumatoid arthritis, arteriosclerosis with hemiplegia or Parkinsonism. No significant change in the basic disease of this group was noted throughout the study.

Eight young normal females (either nurses or internes, 29 to 38 years of age) with gray or graying hair, comprised the second group. These individuals were not patients. The first group was subdivided into 3 sub-groups; 7 persons

received 100 mg. Ca.P. plus 50 gm. of brewer's yeast; 5 persons received 200 mg. of PABA plus 50 gm. of brewer's yeast daily; the remaining 7 received 100 mg. Ca.P., 200 mg. of PABA and 50 gm. of brewer's yeast daily.* The first group continued their medication for 8 consecutive months. In the second group, 6 persons received 100 mg. Ca.P., 200 mg. of PABA and 50 gm. of brewer's yeast daily (1 was irregular); while 2 received just the 100 mg. Ca.P. and the 200 mg. of PABA daily. They remained under treatment for 6 consecutive months.

The third group consisted of 6 normal white females, whose ages ranged from 33 to 42 years. This group was observed by Dr. Elaine P. Ralli at the Metabolism Clinic of the New York University College of Medicine Clinic. The patients were all prematurely gray, and the gray hair had been present for 10 to 15 years. They were given 20 mg. Ca.P. plus 3.5 gm. of yeast concentrate daily for periods of 6 to 10 months.* Photographs were taken at the beginning and end of the experiment, and hair samples were taken at monthly intervals. These were observed by Dr. Ralli at least every 4 weeks. There was no apparent ill-effects from any of the drugs, except for occasional nausea which was probably due to the yeast.

In Groups 1 and 2, at the beginning of the experiment, photographs of the head and samples of hair from a given area were taken from each subject. This was repeated in the middle and at the end of the experiment. Color photographs of the hair samples of selected individuals were taken later. In addition, the same two observers saw these patients at least every 4 weeks and notations were made. At the end of the experiment, the photographs, samples of hair and opinions as to change in color were compared.

Results. Seventeen subjects failed to exhibit any change (Class I); 14 showed such slight change that its existence and certainly its value to the patient was doubtful (Class II); 2 patients exhibited definite change (Class III).

The photographs of the head were useless because slight changes in distance or lighting made large differences in the apparent color of hair. Hair samples were valuable in discrediting many subjectively favorable notes; a very definite color change must occur before it is apparent in the clippings.

Several changes were noted, (Table 1). The most common was the appearance of a yellow or greenish cast to the gray hair, that usually appeared during the first few months and did not always persist. The next most frequent change was the new growth of scattered wiry black hairs. In several cases there was thought to be an increased luster without actual change in color. In one man (Case No. 18), whose hair was sparse, there was an increase in the number of hairs. In only 2 patients (Cases 5 and 6) was there a significant change in color. Both of these patients were males and suffered from rheumatoid arthritis. Both had had brown hair, the one a red-brown, the other a yellow-brown. Both men noticed the change themselves. The change which was observed tended toward a return to the original color. It became apparent after the drugs had been taken for a period of 2 to 3 months, thereafter increasing slowly in intensity until the drugs were stopped. These men were both in the group that received PABA, Ca.P. and yeast.

* We are indebted to Merek & Co., Inc., through the office of Dr. D. F. Robertson for furnishing us with the Ca.P. and PABA necessary for this study, and to the Vitamin Food Co., Inc., for the brewer's yeast and photographs. The yeast concentrate used by Dr. Ralli was supplied by the Freeda-Agar Products Co., New York.

TABLE 1.—RESULTS OF EFFECT OF CALCIUM PANTOTHENATE AND PARAAMINOBENZOIC ACID ON THE GRAY HAIR OF HUMANS (OLDER GROUP)

Patient, age and sex	Medication	Objective change		Subjective change	Class
		Hair	Picture		
1. J.H. 65 M.	Yeast Ca.P. PABA	? Darker	No change	Sl. incr. number hairs	II
2. H.H. 35 M.	"	Grayer	"	? Grayer	I
3. J.McL., 1 23 M.	"	No change	"	No change	I
4. R.R. 72 M.	"	"	"	"	I
5. J.Sch. 58 M.	"	Def. change to red-brown	"	Def. darkening along sides of part	III
6. A.S. 61 M.	"	Def. change to red-brown	"	Very def. red change	III
7. J.S. 62 M.	"	Sl. darker	"	Sl. late yellowing	II
8. M.M. 57 F.	Yeast PABA	Lighter than control	"	Early greenish change	II
9. R.McM. 61 F.	"	Whiter than control	"	Early scattering dark hair; then no change	II
10. M.N. 67 F.	"	No change	"	No change	I
11. P.T. 52 F.	"	"	"	Early dark streak over crown; then no change	II
12. F.D. 62 M.	"	"	"	? Scattering of dark hairs	II
13. T.O'T. 65 M.	Yeast Ca.P.	Lighter than control	? Darker	Sl. golden change	II
14. M.D. 58 F.	"	? Darker	No change	Sl. early yellowing	II
15. G.D. 68 F.	"	Def. yellow early; then return to control	"	Def., temporary, early yellowing	II
16. J.F. 85 M.	"	No change	"	No change	I
17. F.K. 66 M.	"	Sl. darker	"	Sl. increase number of dark hairs	II
18. J.McL., 2	"	? Darker	"	No color change, def. in- crease number of hairs	I
19. M.M. 73 M.	"	No change	"	No change	I

None of the younger subjects (Tables 2 and 3) showed a definite change. In 2 young women with pale red hair, there was an apparent but temporary deepening of the red color. The hair developed a yellow or greenish cast in some cases and there was some scattered new wiry black hairs seen, but the changes were not sufficient to be of practical value.

In the third group, none of the subjects exhibited any demonstrable change in the color of their hair; 2 subjects thought that their scalp was less scaly.

TABLE 2.—RESULTS OF EFFECT OF PABA AND Ca.P. ON GRAY HAIR OF YOUNG WOMEN

Patient, age and sex	Medication	Objective change		Subjective change	Class
		Hair	Picture		
1. M.C. 35 F.	PABA Ca.P.	None	Grayer*	Yel. tint early, ? more gray later	I
2. E.N. 35 F.	Yeast PABA Ca.P.	Grayer	...	No change	I
3. E.C. 33 F.	"	? Darker	...	Sl. more red early, no effect on gray	II
4. A.A. 33 F.	PABA Ca.P.	? Darker	...	Yel. tint early, sl. darken- ing at temp.	II
5. M.B. 36 F.	Yeast PABA Ca.P.	None	Grayer*	Yel. tint early, ? darken- ing of gray	II
6. M.H. 34 F.	"	Yel. tint	Grayer*	Red? more red	II
7. M.Kv. 29 F.	(Irreg.)	None	Grayer*	? Darkening	I
8. M.Kd. 38 F.	"	More gray	...	Sl. darkening	I

* Follow-up photographs taken with different lighting, etc., so that all hair appears much more gray.

TABLE 3.—RESULTS OF EFFECT OF Ca.P. ON GRAY HAIR OF YOUNG WOMEN

Patient, age and sex	Medication	Duration of treatment	Objective change		Subjective change	Class
			Hair	Picture		
M.B.M. 42 F.	20 mg. Ca.P., 3.5 gm. con- cent. yeast	10 months	Grayer	No follow up	None	I
S.S. 37 F.	"	10 "	No change	Darker ?	Scalp better, tex- ture better, yel- low gray	I
A.T. 35 F.	"	10 "	"	More gray	Scalp better, no change in color	I
M.M. 33 F.	"	6 "	"	No follow up	No change	I
M.L. 40 F.	"	10 " (irregular)	"	"	"	I
C.G. 38 F.	"	10 months	Grayer	No change	"	I

Discussion. That only 2 of the 33 persons with gray hair exhibited a definite return of previous color while taking PABA and Ca.P. is of interest for at least two reasons. It suggests that a deficiency of PABA or Ca.P. or both, can under certain circumstances be at least one factor in the development of gray hair. Which substance is responsible is not clear, since both drugs were given to the 2 individuals in which change was observed. After the medication was stopped, the hair gradually became grayer again, a fact which makes the observation secure. What is perhaps of more interest, is that the numerous failures lead one to the conclusion that, for the most part, graying of the hair is dependent on some other train of events.

Martin¹² believes that the ratio of PABA to P.A. is important. He feels a preponderance of PABA favors graying. Pfaltz²² found that the addition of P.A. to the diet of rats deprived of this vitamin par-

tially restored gray color. She found that when PABA was added, the color was restored quicker. This investigator also found that Inosital enhanced the pigment-restoring properties of P.A., although Emerson and Evans⁴ did not find that Inosital significantly improved results over Ca.P. alone. Sieve²⁹ pointed out a possible relationship between PABA and hormones in the graying of hair. Gerstl, Lustig and Goldfarb⁸ indicated that sex had a definite influence in the incidence of nutritional achromotrichia in mice. Forbes⁶ reported that estrogen implanted pellets produced local pigmentation of fur in albino rats, while testosterone dipropionate failed. All this work however, is in an early stage.

It is important also to point out that the indiscriminate use of PABA in humans may be followed by toxic reactions. Scott and Robbins²⁶ found PABA to be poisonous to mice and dogs and less toxic to rats. In dogs, oral doses greater than 1 gm. per kilogram of body weight may cause death. It has also been found^{5,30,31} that PABA inhibits bacteria-static action of sulfonamide drugs, and should therefore not be given when it is necessary to use these drugs.

Conclusions. In a group of 19 elderly individuals with gray hair, only 2 exhibited a significant change in color during an 8 months period of administration daily of 100 mg. calcium pantothenate; 200 mg. paraaminobenzoic acid, and 50 gm. of Brewer's yeast. Both were men.

In a group of 8 younger individuals who received the same dosage for 6 months (2 of the 8 omitted Brewer's yeast), and in a group of 6 younger individuals who received 20 mg. calcium pantothenate and 3.5 gm. of concentrated yeast daily, none developed any decrease in the gray color of their hair.

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TIME-ACTIVITY CURVES OF GLOBIN INSULIN WITH CLINICAL APPLICATIONS

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In the study of any new insulin preparation it is important to determine the total duration of action, and the activity per hour. The time-activity curve has proved a useful method for such study and has been described in detail in previous communications, with reference to regular and protamine zinc insulins.^{4,5,7} In brief, after the injection of the dose of insulin to be studied, glucose is given by mouth at variable intervals in the amount required to keep the blood sugar within the physiologic range (80 to 120 mg. per 100 cc.) as determined by repeated blood sugar determinations. In the severe diabetic, with a fasting insulin requirement⁸ the rise of the blood sugar when insulin effect is over gives a sharp end-point for the duration of action.

While several studies of globin insulin have appeared in the literature they have considered blood sugar curves in (1) the fasting state,¹ (2) with diet,^{5,2} and (3) with constant 2-hourly feedings of glucose.⁸ The present report is a study of the time-activity function of globin insulin, with the clinical application of the results to the optimum arrangement of the diet. The studies include: (1) a summary of 8 time-activity curves, with doses of globin insulin ranging from 10 to 80 units, (2) comparison of the time activity curves of the same dose of regular, protamine zinc and globin insulin in 2 patients, (3) globin insulin curves in 14 patients on a regular diet, and (4) out-patient progress records of 16 patients on globin insulin.

In the majority of instances, blood sugar determinations were made on oxalated venous blood by a modified Folin-Wu micro method.

Time-activity Curves. Figure 1 shows the activity of 80 units of globin insulin in a 14 year old white boy, a severe diabetic. The fall of the blood sugar from 251 to 116 mg. per 100 cc. in the first 5 hours of study, indicates a small insulin activity in the first few hours after

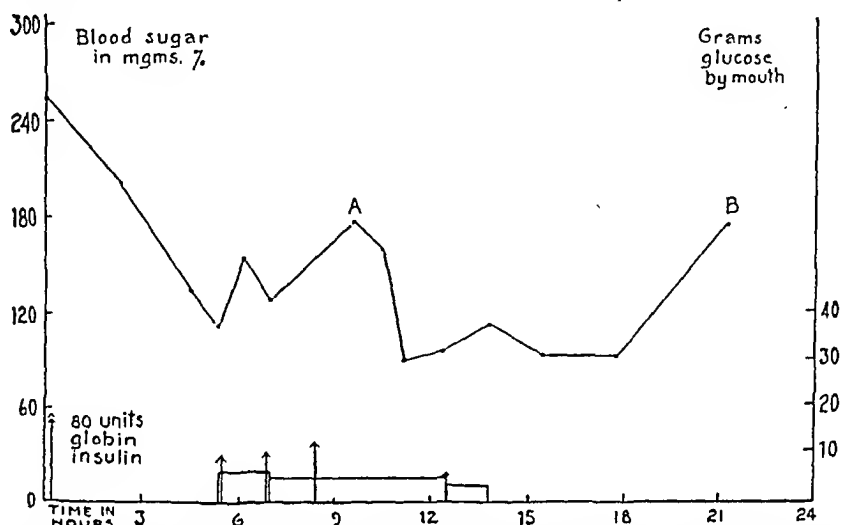


FIG. 1.—Time-activity curve 80 units of globin insulin. Point A: Too much glucose given at this point so blood sugar allowed to return to normal before next dose of glucose. Point B: End of appreciable activity. Single tipped arrows indicate amount of glucose given at that time, in all figures. Boxes represent the amount of glucose, calculated as grams per hour, in all figures. Double tipped arrows represent the time insulin was given, in all figures.

D. R. White male 14, No. 791-326. Diabetic of 1 year's duration. Severe diabetic in good control prior to test on regular insulin 50-30-30; protamine zinc insulin 35-0-0. Diet: C, 275; P, 100; F, 90. Preparation for test: Day before test, protamine zinc insulin was not given. Insulin day before test: regular insulin 50-30-20, and 20 at midnight, with a glass of milk, in addition to diet. No food day of test, except glucose by mouth as indicated in figure.

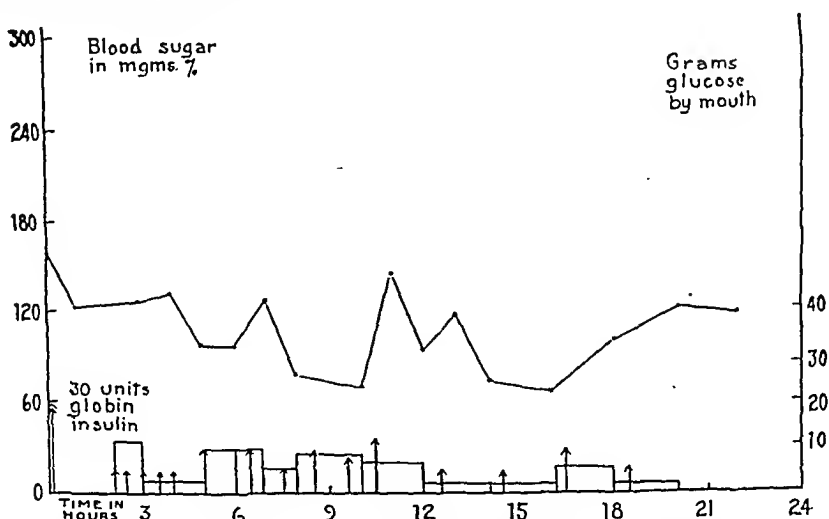


FIG. 2.—Time-activity curve 30 units of globin insulin. H. R. White male 57, No. 810-294. New, untreated diabetic. Controlled without insulin on diet: C, 150; P, 65; F, 80. Preparation for test: none. No food day of test, except glucose by mouth, as indicated in figure.

injection. From the 6th to the 13th hours, 37 gm. of glucose was given to balance insulin activity. At point *A* the amount given was in excess of the requirement, as indicated by the rise of the blood sugar. The peak activity is clearly between the 6th and 9th hours, as the largest amount of glucose was given in this period. The end of activity is sharp, with a rise of the blood sugar from 91 mg. per 100 cc. to 176 mg. per 100 cc. (point *B*), between the 18th and 21st hours after insulin injection. (No glucose was given by mouth after the 12th hour.)

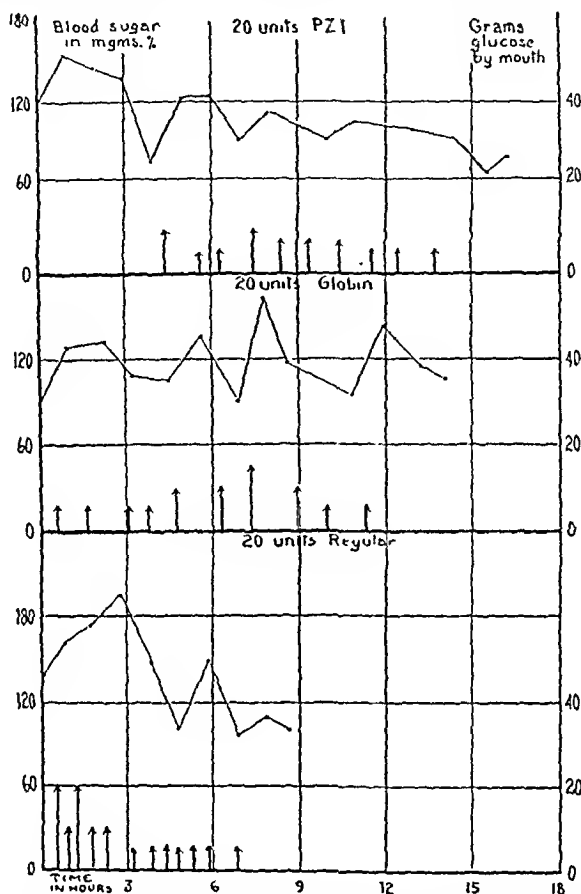


FIG. 3.—Comparison of the time-activity function of 20 units of regular, globin and protamine zinc insulin. Twenty units of regular, globin and protamine zinc insulin, respectively, given at 0 time on graph.

J. S. Mexican male 46, No. 679-103. Known diabetic 4 years. Well controlled on 30 units protamine zinc insulin. Diet: C, 175; P, 70; F, 80. Preparation for test: Day before each test protamine zinc insulin was discontinued and regular insulin 10-10-10 was substituted. No food day of tests, except glucose by mouth as indicated.

Figure 2 in contrast, shows the activity of 30 units of globin insulin in a 57 year old white male—a very mild diabetic. Although this patient was controlled on diet alone, this fact does not change the general configuration of the curve after the injection of insulin. Even non-diabetics can show peak points of action of injected insulin over and above the endogenous secretion. The total amount of glucose handled in any diabetic will depend not only upon the injected dose,

but upon the amount of the effective endogenous insulin. Ninety-five gm. of glucose was required to balance insulin activity, with the blood sugar level between 67 and 144 mg. per 100 cc. The peak of activity lies between the 5th and 10th hours. The end-point of activity is not clearly indicated, as the patient did not have a fasting insulin requirement. However, there is no appreciable effect after the 20th hour.

TABLE 1.—TIME-ACTIVITY FUNCTION OF GLOBIN INSULIN

Name	Usual insulin dose in units Diet C-P-F ¹ in gm.	Dose of globulin insulin in units	Peak of action in hrs.	Duration of significant activity	Total gm. of glucose by mouth to balance activity	No. of hrs. of experiment
1. T. G. 62 Colored male No. 240-338 ²	10 PZI ³ 270-95-95	10	6-8	?	50	11
2. J. S. 45 Mex. male No. 679-103	30 PZI ⁴	20	5-10	13+	75	14
3. J. S. 40 Mex. male No. 276-524	30 PZI 250-90-80	20	5-12	14+	90	15
4. H. B. 57 White male No. 810-294	No insulin 150-65-80	30	5-10	20	95	22
5. J. D. 17 White male No. 250-724	RI ⁵ 40-20-40 PZI 40 300-100-100	40	7-13	18+	95	21
6. D. S. 33 White male No. 631-831	RI 25-10-15 PZI 0-0-10 250-85-80	40	10-20 ? ⁶	22+	127	22
7. W. H. 15 Colored female No. 597-734	RI 25-0-0 PZI 0-0-40 200-100-60	60	12-19 ? ⁶	22+	20	22
8. D. R. 14 White male No. 791-326	RI 50-30-20 PZI 35 275-100-90	80	6-9	18	37	21

KEY: ¹ C, carbohydrate; P, protein; F, fat in all tables.

² Permanent hospital file No.—in all tables.

³ PZI, protamine zinc insulin; RI, regular insulin; CZI, crystalline zinc insulin—in all tables.

⁴ PZI discontinued 24 hours before test with globin insulin in all patients except No. 1.

⁵ Largest amounts of glucose given late (10th to 20th hour), with blood sugar of 30 mg. per 100 cc. at 18th hour.

⁶ Difficult to tell peak as only 2 doses of glucose given—5 gm. at 6th hour and 15 gm. at 15th hour.

The activity of 20 units of globin insulin in a 46 year old Mexican male, a mild diabetic, is seen in Figure 3 (middle curve). During the first 4 hours after injection activity is present, as an hourly dose of 5 gm. of glucose caused little change in the blood sugar level. The peak

of activity occurs between the 5th and 10th hours. Activity is slight after the 13th hour. The blood sugar level fell only 10 mg. between the 13th and 14th hours, and no glucose was given after the 11th hour. This patient also shows no sharp rise of the blood sugar at the end of activity, as he is a mild diabetic with no basal insulin requirement.

Table 1 summarizes the results in the 8 patients on whom time-activity curves were run. The tests were conducted in similar fashion to those traced in Figures 1 and 2. In the majority of cases the peak of action occurred between the 6th and 10th hours, with the end of appreciable activity between the 14th and 18th hours.

Figure 3 shows the striking difference between the time-activity curves of regular, globin and protamine zinc insulins in the same patient. The regular insulin has its peak of action between the 1st and 4th hours, with the end of significant activity between the 7th and 9th hours. A total of 105 gm. of glucose was given to balance the insulin action. In contrast, the peak of action of the globin insulin is 5 to 10 hours, with little activity after the 14th hour. Seventy-five gm. of glucose were given to balance insulin activity. With the protamine zinc insulin the onset of appreciable activity is delayed, with the peak of action between the 7th and 11th hours. Some activity is still present at the 16th hour. Sixty-two and a half gm. of glucose were given to balance insulin activity.

Similar results were obtained in a second patient, in whom the time-activity curves with the same dose of regular, globin and protamine zinc insulin were made.

Blood Sugar Curves With Globin Insulin and Diet. Table 2 summarizes studies on 14 patients on their regular diets with one dose of globin insulin. Five or six blood sugar determinations were made throughout the 24-hour period: fasting, $1\frac{1}{2}$ to $2\frac{1}{2}$ hours after each meal, to obtain postprandial rises; and at 4 P.M. and midnight, for possible low points. Quantitative urine sugars* for the 24-hour period were also run. Seven of the patients received a mid-afternoon feeding, while 7 did not.

In general, the results show that the usual time of occurrence of hypoglycemia with globin insulin lies between 2 P.M. and midnight. Thus, 2 patients had blood sugar levels under 50 mg. per 100 cc. at 2 P.M.; 3 patients had blood sugar levels under 80 mg. per 100 cc. at 4 P.M.; 1 patient had a severe insulin reaction at 10:30 P.M.; and 3 patients had blood sugar levels under 65 mg. per 100 cc. at midnight. In only 1 patient was the fasting blood sugar level under 80 mg. per 100 cc., and no patients had insulin reactions between midnight and breakfast.

The majority of the patients showed a marked postprandial rise of the blood sugar after breakfast (67 to 124 mg. per 100 cc.) despite the fact that all the patients received a light breakfast—one-sixth to one-fifth of the total carbohydrate.

The milder diabetics (Cases 1, 4, 6, 7, 9, 10) showed fairly smooth 24-hour blood sugar curves, and were considered to be moderately well controlled, although certain adjustments of insulin and diet were

* Urine sugars were determined by the quantitative Benedict method.

9. R. T. 35 Mexican male No. 820-719	30	300-90-80 ^f	...	148 0	194 0	125.0	200.0	125 0	133 0	3
10. J. M. 78 White male No. 753-322	35	150-60-80 ^a	98 5	106.0	190.0	...	71.9	41 1	...	Not determined
11. E. D. 55 White male No. 820-882	40	300-95-120 ^d	...	416 0	198.0	119 0	127.0	56 0	240.0	16
	40	300-95-120 ^d	347.6	421.2	41 0	...	105.0	81 0	333 0	32
12. J. D. 38 White female No. 238-170	40	225-80-70 ^f	308 0	266 6	133.3	75 5	248.0	396 0	333 0	76
13. M. D. 83 White female No. 847-199	80	150-60-80 ^b	...	236 6	261 4	224 8	338 0	250 0	119 0	Incontinent
14. P. A. 53 White female No. 825-066	80	130-100-120 ^a	...	200 0	266 6	275 8	272 0	245 0	207.2	21

KEY:

- ¹ All patients except Nos. 6, 7, 8 on globin insulin at least 4 days before test.
- ² Arrangement of carbohydrate in diet:
 - ^a 1/5 breakfast; 2/5 lunch; 2/5 dinner; with or without small bedtime feeding.
 - ^b 1/6 breakfast; 1/3 lunch; 1/6 mid-afternoon; 1/3 dinner.
 - ^c 1/6 breakfast; 1/3 lunch; 1/6 mid-afternoon; 1/4 dinner; 1/12 bedtime.
 - ^d 1/6 breakfast; 1/3 lunch; 1/12 mid-afternoon; 1/3 dinner; 1/12 bedtime.
 - ^e 1/5 breakfast; 1/3 lunch; 1/10 mid-afternoon; 2/5 dinner; ? bedtime feeding.
 - ^f 1/5 breakfast; 1/5 lunch; 1/10 mid-afternoon; 2/5 dinner; 1/10 bedtime.
 - ^g A—? arrangement, but interval feedings at 3 P.M. and 9 P.M.
- ³ B—1/5 breakfast; 3/10 lunch; 1/10 mid-afternoon; 1/3 dinner; 1/10 bedtime. Just as breakfast finished.
- ⁴ Severe insulin reaction requiring intravenous glucose at 10:30 P.M.
- ⁵ 10 to 10:30 P.M.
- ⁶ Afternoon feeding not eaten.

necessary to meet occasional low blood sugar points: 2 P.M., 4 P.M., and midnight.

Patients 2, 3 and 5 showed wider fluctuations of the blood sugar curve due to moderate, transient postprandial rise of the blood sugar curve.

In 4 severe diabetics (Cases 11, 12, 13, 14) control was very poor on one dose of globin insulin due to marked postprandial rises of blood sugar, and also low points in the afternoon or midnight, despite interval feedings. The globin insulin was not sufficient to control the fasting requirement in No. 11, as the blood sugar rose from 81 mg. per 100 cc. at midnight to 333 mg. per 100 cc. before breakfast. Patients 8 and 13, on the other hand, had a marked fall of the blood sugar from midnight to 6 A.M., even with marked postprandial hyperglycemia.

TABLE 3.—COMPARISON OF GLOBIN AND PROTAMINE ZINC INSULIN WITH DIET

Name	Insulin in units	Diet C-P-F ¹	Blood sugar in mg. per 100 cc.					24 hr urine sugar in gm.
			Fasting	2 hrs. after breakfast	2 hrs. after lunch	2 hrs. after dinner	Midnight	
1. M. P. 13 White female No. 772-531	35 PZI	200-100-70	64.5	76	111	135.1	47.6	0
	20 Globin ²	200-100-70	109.0	106	47	132.0	99.0	0
2. J. M. 78 White male No. 753-322	45 PZI	150-60-80	74.0	158	164	198.1	121.1	Sl. tr.
	35 Globin ²	150-60-80	98.5	166	190	71.9	41.1	0
3. J. S. 40 Mex. male No. 672-920	30 PZI	250-90-80	67.0	148	182	150.4	103.6	?
	30 Globin ³	250-90-80	80.0	150	173	220.0	92.6	0
4. J. S. 45 Mex. male No. 679-103	30 PZI	175-70-80	82.0	129	138	143.9	127.4	0
	30 Globin ³	175-70-80	133.0	200	142	121.0	80.6	0

KEY: ¹ Arrangement of carbohydrate in diet: 1/5 breakfast; 2/5 lunch; 2/5 dinner; ? bed-time feeding.

² On globin insulin 5 days before test.

³ On globin insulin 2 days before test.

Five patients (Nos. 1, 3, 4, 5 and 10) have been followed in the outpatient clinic for over 6 months, and have been in fair to moderate control during this period.

Four patients were studied on diet and protamine zinc insulin, and on globin insulin (Table 3). In 1 patient the dose of globin insulin was 15 units less than the protamine zinc insulin; and in another, 10 units less. In the other 2 patients, the same dose was used. In all 4 cases the fasting blood sugar level with protamine zinc insulin was lower by 13 to 51 mg. per 100 cc. than with globin insulin. In 3 of the patients on protamine zinc insulin, the lowest blood sugar of the 24-hour curve occurred fasting, in the other at midnight. The lowest peak of the globin curve occurred at midnight in 3 cases; and in the middle of the afternoon in the other. Except for the differences pointed out above, the general configuration of the curves was quite similar.

Table 4 summarizes the out-patient clinic records of 16 patients. Eight of these patients were in good or moderately good control, *i. e.*, excreted less than 10% of the carbohydrate intake in the 24-hour urine sample in three-fourths of the clinic visits. In this group the doses ranged from 10 units to 50 units of globin insulin. Five patients were in fair control (spilled less than 15% of the carbohydrate intake), with doses ranging from 20 to 80 units; 3 patients were in poor control (spilled over 20% of carbohydrate intake), with doses of 20 to 80 units of globin insulin, and 2 of these were taken off of globin insulin due to poor control. In certain instances poor control was due to intercurrent infections; in others to poor coöperation. Eleven of the 16 patients had been on 2 to 3 injections of insulin daily. Five of this group were in moderately good control on 1 injection of globin insulin. Three patients were given doses over 70 units; only 1 of these was in moderately good control.

Table 5 gives the time of occurrence of insulin reactions with globin insulin. Only 1 reaction occurred between midnight and 5 A.M. The largest number of reactions occurred between noon and 6 P.M.

Discussion. In accord with others^{1,2,3,5} who have studied globin insulin, we have found that it is an insulin with prolonged activity (more than 18 hours), with a peak of action between 6 and 10 hours in the majority of patients.

It is obvious from the time-activity curves and studies on diet that the duration of appreciable effect, as with protamine zinc insulin,³ is a function of the size of the dose and the severity of the diabetes—that is the amount of the hourly basal insulin requirement. Thus, Patient 8, Table 1, had an end of activity at 18 hours, with a dose of 80 units; while in another patient, No. 6, Table 1, 40 units lasted more than 22 hours. In the studies with diet, Patient 11, Table 2, on 40 units of globin insulin showed a marked rise of the blood sugar between midnight and 8 A.M.; while Patients 13 and 8, Table 2, on 80 and 30 units respectively, showed a marked fall of the blood sugar between midnight and 8 A.M.

As the peak of activity lies between 6 and 10 hours the necessity of a mid-afternoon feeding is obvious. As significant activity may last over 18 hours, certain patients may also require a bedtime feeding. As the activity is small during the first few hours after injection, a light breakfast should be given. (We have found that a diet distribution of 1/6 carbohydrate at breakfast, 1/3 at lunch, 1/6 at 3 P.M. and 1/3 at dinner, with a bedtime feeding as indicated, gives the most satisfactory results in the majority of patients.) In starting a patient on globin insulin, a fasting blood sugar on two successive mornings, and blood sugar determinations at 3 P.M. and midnight, plus urine sugars to cover postprandial rises will give the most information concerning points of hypoglycemia and the best dietary arrangement.

As shown graphically in Figure 3, globin insulin has more carbohydrate handling ability per unit than protamine zinc insulin. This makes possible the use of one insulin in many patients who had previously been on one injection of regular insulin and one of protamine zinc insulin, either in the same syringe or separately injected.

TABLE 4.—CLINIC RECORD WITH GLOBIN INSULIN

Name	Globin insulin in units	Previous insulin dose			No. of months followed	Diet C-P-F ¹	Degree of control ²
		A.M.	N.	P.M.			
1. R. B. 73 White male No. 518-986	10-20	"New diabetic"			5	200-75-80 ^a	Good
2. J. M. 78 White male ^c No. 753-322	15-25	PZI 45			7	150-65-80 ^a	Moderately good
3. E. R. 39 White female No. 605-164	20	RI 20-0-0 PZI 30			12	200-75-100 ^a	Moderately good
4. L. K. 33 White female No. 314-400	20-25	PZI 35			1	200-75-80 ^a	Fair
5. I. T. 30 White male No. 254-813	25-35	"New diabetic"			9	300-90-150 ^c	Good
6. C. B. 5 White female No. 744-053	16-24	RI 15-5-5			6	175-70-80 ^d	Moderately good
7. G. S. 58 White female No. 39-791	20-28	"New diabetic"			4	200-75-80 ^d	Poor to fair
8. R. W. 30 White male No. 134-810	24-30 ⁴	RI 20-0-20			1	175-60-90 ^f	? Fair (infection)
9. M. P. 13 White female No. 772-581	15-40 ⁴	PZI 20-35-0-0			13	175-90-100 ^c	Fair
10. T. H. 13 White male No. 292-338	20-40	CZI 14-18-0-0 PZI 15-25-0-0			6	200-90-95 ^c	Moderately good
11. E. L. 30 White female No. 162-277	20-40 ³	RI 10-0-0 PZI 30-0-0			9	100-60-40 ^f	Poor to fair
12. C. C. 30 White female ⁵ No. 265-807	22½-40	RI 10-0-0 PZI 30-0-0			1	250-90-100 ^b	Poor ⁷
13. H. D. 17 White male No. 798-143	45-50	RI 15-0-20 PZI 0-0-20			1	275-110-120 ^b	Good
14. P. K. 16 White Female No. 790-191	80	RI 35-30-30			1	250-100-60 ^b	Moderately good
15. N. S. 18 White female No. 420-816	80	CZI 25-0-25 PZI 0-0-35			1	175-70-80 ^b	Fair
16. B. B. White female No. 802-266	RI 40 80 .	RI 80-0-0 PZI 60-0-0			1	? ^b	Poor

KEY TO TABLE 4:

¹ Arrangement of carbohydrate in diet:

- ^a 1/5 breakfast; 2/5 lunch; 2/5 dinner; with or without small bedtime feeding.
- ^b 1/6 breakfast; 1/3 lunch; 1/6 afternoon; 1/3 dinner.
- ^c 1/6 breakfast; 1/3 lunch; 1/6 afternoon; 1/4 dinner; 1/12 bedtime.
- ^d 1/6 breakfast; 1/3 lunch; 1/12 afternoon; 1/3 dinner; 1/12 bedtime.
- ^e ? arrangement, but interval feeding at 3 P.M. and 9 P.M.
- ^f ?

² Degree of control graded as % of carbohydrate intake (not including carbohydrate derived from protein) spilled in 24-hour urine:

- Good—less than 5% of intake.
- Moderately good—less than 10% of intake.
- Fair—less than 15% of intake.
- Poor—over 20% of intake.

³ Added 2 to 3 units of regular to globin to decrease burning.

⁴ Occasional small doses of regular taken in addition to globin insulin.

⁵ Taken off of globin insulin.

⁶ Died in hospital 3 months after last clinic visit. Entered in mild acidosis, and died of bronchopneumonia. No details of insulin therapy prior to entry obtained.

⁷ Dose ordered cut in half, due to one severe reaction. This is reason for poor control here.

TABLE 5.—TIME OF OCCURRENCE OF INSULIN REACTIONS WITH GLOBIN INSULIN

Time	No. of patients with reactions
8 A.M. to 12 noon	4 ²
12 noon to 3 P.M.	2
3 P.M. to 6 P.M.	6
7 P.M. to 10 P.M.	1
10 P.M. to 12 midnight	2
12 midnight to 5 A.M.	1 ³
5 A.M. to 8 A.M.	1
Time of reaction unknown	2
Reactions	17 ¹
No reactions	13

¹ Patients may be listed under 2 to 3 different times of day.

² Two of these reactions occurred just before luneh.

³ Reaction occurred in a patient who was working unusually hard on the "swing shift," at 2 A.M.

While activity may be present between the 18th and 24th hours after injection, in the majority of instances this is very much less than the nocturnal activity of protamine zinc insulin. Eleven of 30 patients had significant activity between midnight and 8 A.M. This point has not been emphasized sufficiently previously. However, only 1 patient had an insulin reaction in this period. This is a point of considerable practical importance in insulin-sensitive patients, frequently children, who have been prone to have reactions between 12 midnight and 8 A.M. with protamine zinc insulin.

The obvious value of the clear solution of globin insulin, obviating mixing of a suspension, as with protamine insulin, is of practical importance to patients. Also in our small series, 36, we have had no local reactions other than burning, and no generalized allergic reactions.

Certain disadvantages are apparent from our studies. Patients who are very insulin-sensitive develop too marked an afternoon hypoglycemia despite interval feeding and a large lunch. From a purely practical viewpoint, a mid-afternoon feeding is not possible for many diabetics who work. Severe diabetics who have large dietary insulin requirements cannot be controlled on one injection of globin insulin due to marked postprandial rises of the blood sugar. Also, diabetics

with high fasting insulin requirements do not receive enough hourly insulin activity at night to prevent rise of the blood sugar at night, even with large doses of globin insulin, as 80 units. One disadvantage not previously mentioned is burning on injection. Two patients complained spontaneously of this, and 7 other patients on questioning stated that globin burned more than regular or protamine zinc insulin. The reason for this is not apparent as the pH is in the same range as regular insulin.

In general, we feel that globin insulin has a place in the treatment of selected diabetics. As with any insulin it is important to understand its activity and duration of effect for most intelligent use.

Summary. A. Studies with globin insulin have been made on 36 patients. These included:

1. Eight time-activity curves—doses 10 to 80 units. These showed that the duration varied with the dose and the severity of the diabetes, but in general was 14 to more than 24 hours; average 18 to 19 hours. The peak of activity occurred between the 6th and 10th hours. Onset of activity started within 1 hour of injection but was slow for the first 3 to 5 hours.

2. Comparison of the time-activity function of the same dose of regular, protamine zinc and globin insulin in 2 patients showed that globin insulin was intermediary between regular and protamine zinc insulins as to duration and total carbohydrate-handling ability.

3. Studies with diet—14 patients. The blood sugar curves with diet indicated the necessity for a light breakfast, mid-afternoon feeding, and in some instances a bedtime feeding.

4. Out-Patient Progress records—16 patients (doses 10 to 80 units). The majority of these patients were in fair to good control except for occasional upsets.

B. From these studies we conclude that globin insulin has the following advantages and disadvantages: 1. Advantages: (a) In patients controlled with protamine zinc insulin who had severe nocturnal reactions. (b) In patients controlled on a combined dose of regular and protamine zinc insulin before breakfast—injecting singly or combined. (c) More carbohydrate-handling ability than protamine, with earlier peak of action. (d) Clear solution, obviating mixing.

2. Disadvantages: (a) Too low hourly carbohydrate-handling ability to cover diet in most severe diabetics—doses over 50 units. (b) Too short duration of effect to cover nocturnal insulin requirement of severe diabetics. (c) Burning on injection in an occasional patient.

Appreciation is expressed to Dr. Solomon Strouse and Dr. Howard West for the use of patients on their services at the Los Angeles County Hospital; and to Burroughs-Wellcome & Company for the supply of globin insulin for investigational use.

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EOSINOPHIL LEUKEMIA

WITH REPORT OF A CASE

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THE existence of eosinophil (eosinophilocytic) leukemia as an entity distinct from myelogenous neutrophil leukemia has not been unequivocally established. A major reason for questioning its separate identity has been the morphologic maturity of eosinophils seen in the peripheral blood and bone marrow of proposed cases, as contrasted with the large numbers of immature and atypical cells found in the more familiar types of leukemia, in "leukemoid" eosinophilic reactions, and in so-called "mixed" leukemia. The issue is complicated also by the well known tendency for eosinophil cells, both mature and immature, to become increased though not dominant in chronic myeloid leukemia.

Eosinophilic leukemia, loosely interpreted, may not be as rare as is suggested by the meager number of instances which have been reported.^{1,4,6-10,12,13,15-18} For example, Doan and Reinhart,³ who analyzed 317 patients with leukemic syndromes, classified 3 as chronic eosinophilic myelogenous leukemia, and described one other having both eosinophilic and basophilic granules within the same malignant myelocytes, as "mixed" chronic myelogenous leukemia. The lack of certainty which attends the diagnostic interpretation of leukemia with eosinophilia prompts this presentation of another case.

Case Report. An 11 year old colored boy was admitted December 17, 1943 to King's Daughters Hospital, Norfolk, Va., with progressive weakness, edema of legs and abdomen, and shortness of breath following an acute eruptive illness a month previously termed "measles." Prior to November, 1942, he was said to have been in good health, though a photograph taken the preceding summer showed him with shoes unlaced, suggesting that swelling of the feet was present even then. He was weak and undernourished and of average height. He had a harsh, moderately productive cough. The nose, cheeks and submaxillary areas were swollen. The upper eyelids were puffy and the eyes lacrimated constantly. The left lacrimal gland was enlarged and palpable. Swollen pale turbinates occluded the nasal passages. The posterior cervical lymph nodes were slightly enlarged, but no other superficial nodes were palpable. Breathing was moderately rapid. Roentgenography showed irregular increased densities throughout the entire lung fields, most prominent at the bases. There was pleural thickening and an enlarged cardiac shadow. Blood pressure was 90/70. The abdomen was not distended but moderate pitting edema of the anterior abdominal wall extended up to the xiphoid. The liver extended two fingers breadth below the costal margin. The spleen could not be felt; there were no palpable abdominal masses. The legs and thighs were

swollen and edematous, the right thigh being larger than the left. Body temperature fluctuated between 36.5° and 38° C. Laboratory studies are shown in Table 2. The patient was kept in bed and given symptomatic treatment. Because of the low blood protein level 500 cc. of blood plasma was administered on December 23, followed by disappearance of the respiratory distress and most of the edema within 72 hours. The thigh circumference, however, continued prominent. He was discharged on January 6 after relief of the immediate symptoms, but rehospitalized from January 19 to January 27 with a recurrence. The pulmonary infiltration was found to have subsided and the cardiac shadow was practically normal in size. No clinical improvement occurred during this admission and the subsequent course at home was progressively downhill.



FIG. 1.—Photograph of the patient taken on March 25, 1943. Note the emaciation of the arms and chest, swelling of the lips, eyelids and salivary areas and open mouth (mouth breathing).

From March 13, 1943, until death on April 17, the patient (Fig. 1) was at the U. S. Marine Hospital, Norfolk, Va. Emaciation, weakness, edema of the lower extremities, rapid respirations, productive cough, swelling of the nose, cheeks, lips and submaxillary areas were prominent features. The submaxillary and sublingual glands were large, hard and discrete. Fine and coarse inspiratory and expiratory râles were audible. The spleen was not felt. The patient had a hearty appetite and consumed large quantities of food. The leukocyte count fluctuated from 126,000 to 194,000 with an eosinophilia from 80 to 94% (Table 1). On March 18 the total blood protein was 5.8 mg. per 100 cc., with 3.4 mg. globulin and 2.4 mg. albumin. Because of this low value, six 250 cc. doses of blood plasma were administered intravenously in a 10-day period, beginning on March 20. During this period the edema subsided, except in the thighs, and the blood protein picture became normal (Table 2): The following laboratory examinations showed results within the normal range; Blood sugar, blood chlorides, blood urea, blood uric acid, blood cholesterol, blood cholesterol esters, icteric index, bleeding time, clotting time, reticulocyte count, platelet count, hematocrit, serologic tests for syphilis, tuberculin patch test, skin test for ecchinococcus, heterophil reaction, fragility test, bromsulphthalein test, and feces for ova and parasites. Two electro-

cardiograms were normal. Roentgen films (Fig. 2) on March 15 revealed rather dense sharply circumscribed shadows throughout both lung fields and enlargement of the heart. Repeat examinations on March 23 and April 6 revealed an increase in these lung field shadows, especially in the lower lobes. Radiography of the skeleton, including the pelvis, showed no abnormalities. The nasal discharge contained eosinophils. Studies of the bone marrow by sternal puncture (Table 3) revealed a predominance of eosinophils with more young forms than in the peripheral blood. On April 16, biopsy of a posterior cervical gland was performed under local anesthesia. The following morning at 3:30 A.M. respirations suddenly ceased.

TABLE 1.—REPRESENTATIVE DIFFERENTIAL CELL COUNT OF PERIPHERAL BLOOD (TOTAL COUNT 126,000) (DONE ON MARCH 25, 1943—500 CELLS COUNTED)

Type of cells	%
Eosinophils	82.0
Promyelocytes	0.0
Myelocytes	0.4
Metamyelocytes	0.6
One-lobed (staff) cells	19.6
Two-lobed cells	43.0
Three-lobed cells	15.2
Four-lobed cells	3.0
Six-lobed cells	0.2
Neutrophils	4.4
Staff cells	0.4
Mature cells	4.0
Basophils	0.4
Monocytes	4.0
Lymphocytes	9.2

Necropsy. The liver was large, with yellow-red parenchyma. It weighed 1300 gm. The spleen was not enlarged, weighing 90 gm. Its pulp was red, soft and grossly not infiltrated. The small lymph follicles were not unusually abundant. The kidneys, adrenals and gastro-intestinal tract showed no changes. The mesentery was wasted and contained small normal sized lymph nodes. A broad chain of enlarged unusually abundant retroperitoneal lymph nodes extended from the pelvis up through the diaphragm, becoming continuous with a mass of large mediastinal nodes in the thorax. Some nodes about the lesser curvature of the stomach and the branches of the celiac axis were similarly enlarged. The average length of these large nodes was 2 to 3 cm. All were soft, discrete and homogeneously gray on section.

A wide sheet of yellow-gray infiltrative tissue, 1 to 2 cm. in thickness, was found in the extraperitoneal fascia of the pelvis, contiguous with the bones but extraperiosteal. This tissue was edematous in areas and not always of the same thickness. Neither bladder nor rectum was invaded. The infiltration continued through the large foramina and beneath the inguinal ligaments down into the soft tissue of both thighs. A great mass of large discrete lymph nodes was found in the right inguinal and femoral region, enveloping the nerves and blood-vessels and extending peripherally along their courses. The upper thigh muscles were pale and infiltrated with poorly defined yellow streaks. Similar streaks extended the entire length of the right iliopsoas muscle. The infiltrative changes in the thigh were confined beneath the fascia lata and did not involve the subcutaneous fat. The pleural sacs and the pericardium each contained 100 cc. of clear yellow fluid. The thymus was shrunken. The heart was dilated and weighed 220 gm. In the posterior mediastinum numerous large lymph nodes extended from the diaphragm to the clavicles and also laterally along the bifurcation of the trachea. The lungs were emphysematous and together weighed 360 gm. They contained some gray-red foci of consolidation posterior and inferior to the lower major bronchi. The bronchopulmonary nodes were large and the bronchial walls were thickened. The bronchi were dilated and contained yellow-gray muco-pus. The sphenoid and

TABLE 2.—SIGNIFICANT DATA ON BLOOD STUDIES IN CASE OF EOSINOPHILIC LEUKEMIA

Date:	December				January				March				April			
	17	19	28	29	5	21	15	18	20	22	26	27	31	2	7	13
RBC (in millions)	3.99	3.72	4.65	4.5	5.0	..	5.0	4.5	4.7	..	4.6	5.0	4.9	4.8
Hb. (in gm.)	11.6	11.2	13.0	13.1	13.3	..	15.3	14.0	14.0	..	13.7	..	13.3	14.4
WBC (in thousands)	..	108	109	121	102	135	194	..	169	138	126	..	143	129	170	190
Eosinophils (in %)	..	81	90	85	81	83	92	..	92	90	85	..	89	..	80	88
Neutrophils (in %)	..	2	3	1	0	2	1	..	1	1	5	..	5	..	4	4
Lymphocytes (in %)	..	17	8	14	16	15	7	..	7	9	9	..	6	..	16	8
Monocytes (in %)	..	0	0	0	3	0	0	..	0	0	1	..	0	..	0	0
Platelets (in thousands)	120	..	150	..	145	155
Total proteins (in gm. %)	5.36	5.8	..	6.7	..	6.5	7.5	7.6	7.4	6.8
Albumin (in gm. %)	2.18	2.4	..	3.9	..	3.4	4.4	4.0	3.7	3.5
Globulin (in gm. %)	3.18	3.4	..	2.8	..	3.1	3.1	3.6	3.7	3.3
A/G ratio (in gm. %)	0.68	0.7	..	1.4	..	1.1	1.4	1.1	1.0	1.1

ethmoid sinuses were filled with green muco-pus. Their lining mucous membrane was thickened, polypoid and discolored. The bones had normal external contours and red succulent marrow.

Microscopy. *Lungs.* The hilar connective tissue was thickened and edematous. The bronchi were abnormally large, with hyperplastic mucous membrane. They contained exudate and the bronchiolar epithelium was rich in eosinophils. The mucous and submucous coats and the supporting tissue of the bronchial glands, as well as the peribronchial fascia and bronchioles, were infiltrated with a mixture of mature eosinophils and faintly basophilic cells having irregular pale staining cytoplasm and large rounded or indented vesicular nuclei. These took the oxidase stain and were judged to be eosinophilic myelocytes. Adult neutrophils and lymphocytes were infrequent. The pulmonary capillaries were distended, some being filled with leukocytes, chiefly eosinophils. Many alveoli were filled with an acute pneumonic exudate, with nearly all the invading cells being mature eosinophils. In other alveoli the walls were thickened and the lumens contracted with organizing tissue occupying the lumens. Eosinophils were abundantly present within their walls.



FIG. 2.—Roentgenograms of chest showing progressive involvement of hilar regions and lower lobes by eosinophilic infiltration, verified by necropsy. A, January 21, 1943; B, April 6, 1943. Note enlargement of the heart shadow. (Photographs by Dr. Robert Drelich, U. S. Marine Hospital, Norfolk, Va.)

TABLE 3.—DIFFERENTIAL CELL COUNTS OF ASPIRATED BONE MARROW
(500 CELLS COUNTED)

Type of cells	%	
	Dec. 20, 1942	Mar. 19, 1943
Myeloblasts	0.8	0.4
Eosinophilic series	65.0	74.2
Promyelocytes A	3.2	1.4
Promyelocytes S	4.9	4.2
Myelocytes	14.0	9.0
Metamyelocytes	9.1	6.4
One-lobed (staff) cells	6.6	12.8
Two-lobed cells	15.1	25.6
Three-lobed cells	9.8	13.6
Four-lobed cells	2.3	1.2
Neutrophilic series	13.0	9.4
Myelocytes	1.0	0.0
Metamyelocytes	1.9	0.0
Staff cells	4.0	2.6
Polymorphonuclears	6.1	6.8
Basophilic myelocytes	—	—
Lymphocytes	10.4	12.2
Monocytes	0.2	0.6
Red cell series	10.2	2.8
Megaloblasts	2.8	1.2
Pronormoblasts	3.7	0.8
Normoblasts	3.7	0.8

Lymph Nodes. The germ centers were hyperplastic and the lymph sinuses filled with lymphocytes. Eosinophils were present in very small numbers inside the node, though infiltrating heavily the pericapsular fascia.

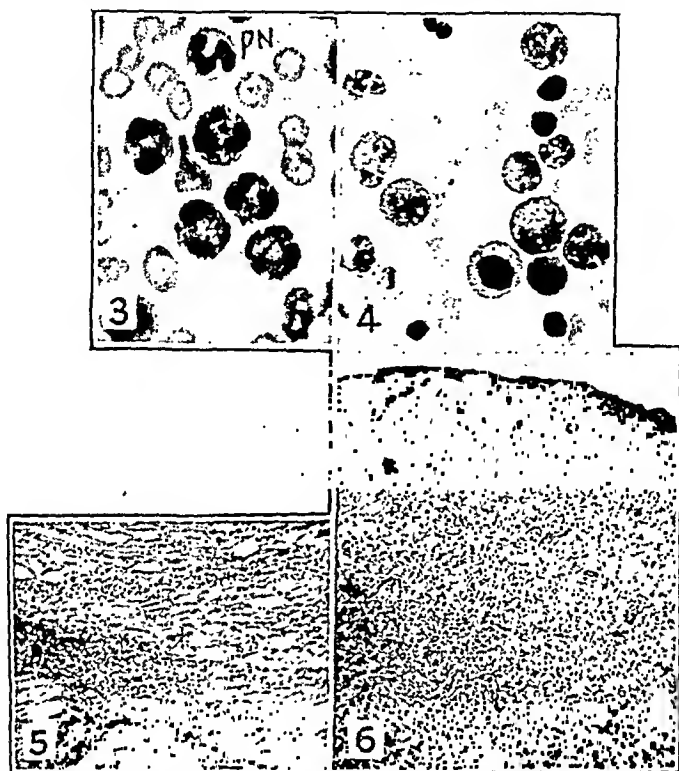


FIG. 3.—Photomicrograph ($\times 1000$) of a typical peripheral blood smear, showing the essentially normal mature appearance of the eosinophils in the circulation. A polymorphonuclear neutrophil is included, demonstrating that the eosinophils are not unusually large.

FIG. 4.—Photomicrograph ($\times 1000$) of bone marrow aspirated December 20, 1942. The larger leukocytes are eosinophil myelocytes, with granular cytoplasm and oval or indefinite nuclei. The nucleus of one cell is hyperchromatic. The smaller leukocytes are more mature forms having "staff" rod-shaped nuclei. Several lymphocytes, one polymorphonuclear neutrophil and one normoblast are also shown.

FIG. 5.—Photomicrograph ($\times 100$) of striated muscle showing leukemic infiltration of the tissue, most marked in the interfascicular fascia.

FIG. 6.—Photomicrograph ($\times 100$) of hypertrophied mucous membrane of splenoid sinus. There is heavy infiltration of the interstices with leukemic cells. Study under higher power shows that many of the eosinophils present are immature and apparently proliferating *in situ*.

Pelvic Fascia. The connective tissue layers were broadened, having a loose mucinoid stroma containing great numbers of infiltrating cells homogeneously distributed. About two-thirds of these cells were mature or nearly mature eosinophils. The majority of the remaining cells were larger, with round or oval nuclei of coarse chromatin structure and a relatively large amount of oxidase-positive basophilic non-granular cytoplasm. The adult eosinophils took the fat stain in frozen sections whereas those less mature did not.

Liver. The individual hepatic cells were hypertrophied with refractile granular cytoplasm. Many eosinophils lay within the sinusoidal spaces and the connective tissue.

Spleen. The Malpighian follicles were small and not numerous; their centers were not hyperplastic. The leukocytic elements of the pulp appeared

somewhat increased. Large numbers of eosinophils were scattered through the sinuses and pulp spaces, most abundant about the periphery of the lymph follicles. The majority of the eosinophils were mature cells, though occasional ones were myelocytes or metamyelocytes.

Bone Marrow. Ribs, vertebræ, sternum, pelvis and skull were identical, with highly cellular marrow spaces and uninvolved trabeculae. The great majority of the myeloid cells were eosinophils with morphology and age distribution essentially the same as in the aspiration counts given in Table 3. Other cells with agranular cytoplasm were present in moderate numbers, uniformly mixed (Fig. 4).

Ilio-psoas and Thigh Muscles. Many muscle bundles were penetrated or compressed by infiltrating areolar tissue. The cells in this invading tissue consisted of eosinophilic granule-containing cells and younger presumably immature eosinophils (Fig. 5).

Sphenoid Sinus. The mucous membrane was thrown up in hyperplastic folds 5 to 20 times thicker than normal. The mucous membrane matrix was composed of loose areolar mucinoid connective tissue, rich in young thin-walled capillaries and heavily infiltrated with eosinophilic leukocytes of all ages. Neutrophils and lymphocytes were uncommon. The sinus contents consisted largely of mucus, infiltrated with degenerated unidentifiable leukocytes (Fig. 6).

Gastro-intestinal Tract. Eosinophils of various ages had densely infiltrated all layers of the stomach, the submucous and muscular coats being several times normal thickness. No changes were noted in the intestine apart from sporadic eosinophils. These cells were abundant also in the retroduodenal fascia.

Diaphragm. The subserosal connective tissue on each aspect and many of the interfascicular layers were infiltrated with eosinophilic cells.

Right Femoral Nerve. Fibers and sheaths were intact, but the enveloping fascia were heavily infiltrated.

PATHOLOGIC DIAGNOSIS. Chronic eosinophilic leukemia, with eosinophilic infiltration of bone marrow, thighs, back muscles, stomach, salivary glands, pelvis, lymph nodes, lungs, nasal mucous membranes, femoral nerve, and other tissues; enlargement of the liver; chronic sinusitis; chronic pneumonia and bronchiectasis; emaciation.

Discussion.—This boy was judged to have had chronic myelogenous leukemia, eosinophilic variety, inasmuch as he showed the major nosologic manifestations of leukemia agreed upon by current authoritative opinion.^{5,11,14,19,20} He suffered from weakness, cachexia and loss of weight progressing to a fatal outcome; the leukocyte count was extremely high (126,000 to 194,000 cells per c.mm.); 80 to 92% of the white cells in the circulation were eosinophils, nearly all mature, to be sure, though occasional young or abnormal forms were demonstrable; the bone marrow, lymph nodes, pelvic fascia, thigh and back muscles, salivary glands, lungs, stomach, nasal mucous membrane and other tissues were infiltrated with myeloid accumulations of eosinophils. None of the other disorders which may give rise to high eosinophilia were known to be present in this patient. An interesting clinical phenomenon was the presence on two occasions of hypoproteinemia with dependent edema, probably secondary to dysfunction of the enlarged liver, and prompt relief of these symptoms by intravenous administration of blood plasma. That such other findings as splenomegaly, marked anemia, architectural destruction of spleen and lymph nodes, hemorrhages, and thrombocytopenia were absent does not seem of sufficient significance to invalidate the diagnosis; these features are

TABLE 4.—REPORTED CASES OF EOSINOPHILIC LEUKEMIA

Author	Age when first seen	Duration of symptoms	Range of WBC	Range of eosinophil (%)	Type of eosinophil in peripheral blood	Organs macroscopically affected
<i>Acute Cases</i>						
Hay and Evans, Case 1 (1929)	41	Less than 3 wks.	72,187 (terminal)	83.7 (terminal)	Mature	Lymph glands, spleen
McCowan and Parker (1932)	45	13 days (?)	154,000-20,000	78.5-?	29.5% myelocytes	Spleen
Stephens (1935)	17	2-3 mos.	130,000	68.6	1% metamyelocytes	Lymph glands, lungs
Forkner <i>et al.</i> (1937)	33	27 days	265,500-118,000 (only figures noted)	82.0-75.0	Many myeloblasts; only 27% mature	Lymph glands, spleen, liver, lungs
<i>Chronic Cases</i>						
Giffin (1919)	31	7½ yrs.	211,000-15,400	90.7-66.3	Mature	Lymph glands, liver, spleen, heart
Shapiro (1919)	48	6 yrs.	236,000-15,700	90.0-48.5	0.0-5% myelocytes	Lymph glands, liver, spleen, lungs
McDonald and Shaw (1922)	46	8 yrs. (alive when reported)	138,250-34,000	82.0-71.4	Mature	Lymph glands, spleen
Harrison (1930)	23	23 mos.	16,000-13,450	60.0-30.0	Mature	Lymph glands, spleen, liver, lungs
Drennan and Biggart (1930)	15	16 mos.	73,170-32,760	70.0-23.0	Mature	Lymph glands, spleen, liver, lungs, left leg
Thomsen and Plum (1939)	11	13 mos.	65,000-3,900*	90.0-0*	62% mature; after irradiation, 81% myeloblasts	Lymph glands, spleen, liver, heart
Goehl (1942)	18	10 mos.	190,900-7,800	88.0-5.0	Mature	Lymph glands, spleen
<i>Unclassified Case</i>						
Stillman (1912)	27	No mention (alive when reported)	165,000-118,000	91.4-85.8	20% metamyelocytes, 2% myelocytes	Lymph glands, spleen, liver
<i>Mixed Cases</i>						
Alexander (1924)	50	9 yrs.	150,200-16,800	36.0-21.5	Mature	Spleen, liver, lungs, heart
Hay and Evans, Case 2 (1929)	53	2½ yrs.	62,180-16,000	55.0-16.1	Mature	Spleen, liver, heart, kidneys

* Due to irradiation.

not universal in any variety of human leukemia. Even though observed symptoms dated back but 5 months, the absence of anemia, the persistence of the platelets at or near a normal level, and the failure of the marrow to show infiltration with primitive blast forms, suggest that this case be classed as chronic or subacute, rather than as acute, leukemia.

A survey of 12 somewhat similar cases that have been reported as eosinophil leukemia, along with the instance here reported, brings out certain significant features (Table 4). Twelve were males. The ages ranged from 11 to 48 years, though 5 were under 20 when symptoms began. Four cases were acute, 8 chronic including the present case, and 1 unclassified. Weakness was complained of by 7, prostration by 3 and gastro-intestinal disturbances by 5. Lymph node enlargement was noted in 10, with 2 others displaying this at necropsy. Ten had splenomegaly clinically and this was found at necropsy in 1 additional case. Hepatomegaly was present in 8, and hemorrhagic manifestations in 5. Five were edematous. Fever was not encountered. Attempts at therapy consisted of irradiation in 1 case, small doses of Fowler's solution in 1, splenic extract in 1, and 2 splenectomies. Irradiation and Fowler's solution caused marked decrease in the leukocytosis. Splenectomy was followed by increase in the number of leukocytes though with some clinical improvement. Death was usually from exhaustion.

As for the blood, 10 out of 12 cases showed anemia during some portion of the disease, usually terminally, though the anemia was severe only in 2. Platelet counts were performed in 2 of the acute cases, one value being 69,000 per c.mm.,¹⁰ the other less than 5000.⁶ In the 4 cases of chronic leukemia where recorded the values ranged from 140,000 to 360,000. The total white count was nearly always high, every case except one⁹ (16,000) having been at one time or another between 65,000 and 312,000 per c.mm.; no instances of transient depression of the total count with an interval phase of aleukemic leukemia were encountered. The mature eosinophils were as a rule typical, with segmented nuclei and densely refractile granules. Several authors commented that the adult cells seemed unusually large, but this distinction must be made with care since the diameter of leukocytes in blood films depends to great extent on the thickness of the smear. Vacuoles in the cytoplasm and granules of irregular size and abundance have been described. In the patient here reported, the adult eosinophils were of normal appearance, but in the myelocytes and metamyelocytes the quantity and maturity of the eosinophilic granulations were not always in the same stage of maturity as were the nuclei. Thus, for example, cells having the nearly mature rod-like nucleus of the staff cell type often contained but few immature eosinophilic and basophilic granules, grouped in one portion of the basophilic cytoplasm. The most common hematologic change has been the migration of immature cell forms—myelocytes, metamyelocytes and stab cells—into the blood stream. Infrequently, these have been numerous, up to 73% of the total eosinophils on one count in Forkner's patient. In

another unusual case¹⁸ 80% of the circulating leukocytes were judged to be primitive myeloblast forms. In several other instances immature cells represented 0.5 to 5% of the differential count. However, in fully half of the cases no immature cells were seen in the circulating blood.

Pathologically, organ infiltration by proliferating eosinophilic myeloid tissue was noted in lymph nodes and spleen in 9 cases, in kidneys 4 times, and invariably in the bone marrow when studied. Pulmonary infiltrations were observed in 6 instances; the Roentgen appearance of these resembled tuberculosis or chronic lung infections. The present patient had heavy invasion of many body structures by eosinophils but a negligible degree of infiltration into the spleen. One other patient in addition to ours—Drennan and Biggart's⁴ 15 year old boy—showed a pelvic mass and involvement of the psoas and leg musculature. Myocardial dilatation with formation of antemortem thrombi within the heart was noted 4 times; Shapiro's¹⁵ case had leukemic infiltration of the heart muscle and Giffin's⁷ showed chronic obliterative pericarditis. In the case here reported many eosinophils were present in the alveolar exudate of chronic pneumonia, in the mucopurulent secretion of bronchiectasis and sinusitis, and in the thickened mucous membrane of obstructed nasal accessory sinuses. The appearance of the exudate suggested that the eosinophils in these areas were actively participating as phagocytic agents of chronic inflammation.

The eosinophil is known to be a type of cell which proliferates readily in the presence of a wide diversity of constitutional disorders. Hence it is unexpected to find this cell more resistant to the inciting agent of leukemia, whatever that may be, than nearly every other kind of leukocyte in the circulation, as attested by the great paucity of such cases on record. Consequently, every patient with prolonged persistent eosinophilia suspected of having leukemia should receive exhaustive study to rule out other known causes of this blood reaction. Even eosinophilic myeloid hyperplasia or infiltration of eosinophils into biopsied lymph nodes are not in themselves pathognomonic signs of leukemia, for, as Bass² experienced, these findings can persist for months in chronic eosinophilia, and then later fade away. Indeed medical progress may disclose some day that clinical pictures of the type discussed here have an infectious rather than a neoplastic origin, and should be classed among the inflammations rather than as leukemia.

Summary.—A case of leukemia in an 11 year old colored male is presented. Clinically there was weakness, emaciation, chronic cough, generalized enlargement of the lymph nodes of the head and neck, hepatomegaly, dependent edema, leukocytosis up to 194,000 cells per c.mm., eosinophilia ranging from 80 to 90% with nearly all mature cells, and decrease in total proteins with inversion of the albumin/globulin ratio. Necropsy demonstrated increase of mature and immature eosinophils in the bone marrow, with infiltration into lymph nodes, pelvic fascia, thigh and back muscles, salivary glands, lungs, stomach, nasal mucous membrane and other tissues. The spleen was but slightly involved. This instance and 12 others found in the hematologic

literature seem to be best characterized as manifestations of leukemic overgrowth of the eosinophil blood cells, though admittedly the nosologic basis for this interpretation rests solely on morphologic evidence.

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PLASMA LIPIDS IN PATIENTS WITH RHEUMATOID ARTHRITIS RECEIVING GOLD SALT THERAPY AND DURING PREGNANCY

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RHEUMATOID arthritis has been studied from innumerable points of view and recently certain pathologic and physiologic states which greatly modify this disease have been clarified. Jaundice and pregnancy are the outstanding conditions which cause, in most instances, an about face in the course of this disease. Hench^{16,17} has reviewed the historical background of the effect of both these factors and presented a clinical analysis of 16 patients with rheumatoid arthritis who have become pregnant during their disease. Fifteen of these "experienced striking, generally complete, relief during pregnancy and for variable periods thereafter." Eleven patients with rheumatoid arthritis who became pregnant have been studied at this hospital.¹ Ten of these noted marked relief of pain and diminution in swelling during the pregnancy. As in Hench's group, most of our patients noticed the ameliorative effect before the 3rd month and this continued until

* On leave of absence.

at least 1 month after delivery and usually longer. Others have made the same observations in scattered cases of pregnancy in rheumatoid arthritides. Two important additions to the problem of study and treatment of rheumatoid arthritis stem from these observations. First, the course of rheumatoid arthritis can be dramatically altered and apparently temporarily reversed by changes in the total metabolism of the body brought about by such pathologic or physiologic states as jaundice and pregnancy; second, nature has provided a signpost which points to a new direction for the investigation of this disease.

Pregnancy produces protean physiologic changes which might be studied in patients with rheumatoid arthritis. We have observed the lack of therapeutic response in female arthritic patients receiving massive doses of the best known hormones of pregnancy (estrogens, progestins and chorionic gonadotropin) administered singly and together.² A review of the physiologic changes in pregnancy that might be the cause of the ameliorative effect revealed that one of the most profound chemical changes was that of a great increase in plasma lipids.^{5,21,23} In view of the lipemia of obstructive jaundice,^{8,9,10,24,25} this fact seemed peculiarly interesting.

The lipemia of pregnancy is due almost entirely to an increase in plasma lipids, the red cells showing but little change. The neutral fat of the plasma begins to increase in the first trimester, while phospholipid and cholesterol rise in the second trimester. At term phospholipid and free cholesterol are each increased 25% and neutral fat over 100% over their value in non-pregnant women. The lipemia revealed no shift in lipid ratios and the iodine numbers of the fatty acids involved indicate no change in their composition; while in birds estrogenic substances have been shown to increase the blood lipid levels,⁷ and Corwin¹² has been able to produce a sustained hyperlipemia in dogs by feeding phospholipids. Attempts to produce lipemia in humans have been unsuccessful and the actual cause of lipemia in pregnancy is yet to be disclosed. Boyd⁵ lists 15 causes for the lipemia of pregnancy, none of which is proven by experimental data. Likewise the increase in blood lipids in obstructive jaundice, untreated diabetes mellitus and severe anemia is unexplained.

Freyberg and his associates³ have published a study in which they compared the partitioned plasma lipids in obstructive jaundice and in patients with rheumatoid arthritis to determine if the increase in serum lipids in the former condition could account for the beneficial effect of jaundice in rheumatoid arthritis. They confirmed previous studies^{13,18,19} that total serum lipids and its fractions are normal in patients with rheumatoid arthritis and concluded that jaundice is not beneficial to arthritic patients by reason of correcting a lipid deficiency, but it is possible that the extremely high levels of total lipids, phospholipids and total and free cholesterol which are present in jaundice may be a factor in causing the beneficial effect of jaundice on arthritis. These workers did not confirm the work of Bruger *et al.*^{14,15} who reported a decrease in total cholesterol with a normal ratio of free cholesterol to cholesterol ester.

In order to extend these studies and determine if there was any peculiarity in the lipemia of pregnant arthritics as compared to normal pregnancy, we have studied 3 groups of patients with active rheumatoid arthritis: (a) those receiving standard non-specific therapy; (b) those receiving the former with added gold salt therapy; and (c) arthritics during pregnancy and after delivery. The patients receiving gold salt therapy (Group b) were included to see if this form of treatment, thought by some workers to be helpful, shifted the plasma lipids in any way.

Procedure. Plasma lipid studies were made on 21 patients with active rheumatoid arthritis as manifested by painful swelling of the joints, anemia, weight loss and increased erythrocyte sedimentation rate, 10 of whom (Group a) received non-specific treatment and 11 the same régime with added gold salt therapy (Group b). In the latter group serial observations were made in the course of treatment—usually at the beginning, halfway through (after administration of approximately 500 mg. of the gold salt), and at the end of treatment (after 1000 mg. of gold salt). In the presence of no specific blood dyscrasia, with normal urinary findings, and in the absence of a history of kidney or liver disease, or of a sensitivity to drugs, these patients received one 25 mg. dose, one 50 mg. dose and 19 weekly doses of 100 mg. each of a soluble intramuscular preparation (gold content, 50%). This gave a total of 1975 mg. over a period of 21 weeks. All the patients were hospitalized for this therapy.

Four pregnant rheumatoid arthritics (Group c) were studied, 3 prepartum and postpartum and 1 during pregnancy. All 4 had activity at the time of conception and enjoyed freedom from arthritic symptoms from 3 months pregnant to a month or more after delivery.

All blood samples were taken after a 15-hour fasting period. The diets of the few out-patients studied were all normal and the remainder (over 90%) had been on the standard house diet of the Robert Breck Brigham Hospital for days or weeks before the sample was taken. Clinical and laboratory studies ruled out hypothyroid, diabetic, nephritic and hemorrhagic lipemia.

Chemical Methods. According to the method of Bloor,⁴ a filtrate of an alcohol ether extract was prepared from 2 cc. of plasma. Aliquots of this filtrate were used for the determination of various lipid fractions. Total lipid and cholesterol were obtained by the sulfuric acid-dichromate oxidation method. Phospholipid phosphorus was determined in duplicate by an unpublished modification of the Fiske-Subbarow aminonaphthol-sulfonic acid-phosphate method adapted to the Klett photoelectric colorimeter.¹¹ The cholesterol ester value was determined by calculation using 68% of total cholesterol, since in normals,^{20,22} rheumatoid arthritics^{3,13,14,15,18,19} and pregnant women^{5,21} this figure has been found to obtain. Total fatty acids, total phospholipid, phospholipid fatty acid, cholesterol ester fatty acid, neutral fatty acid, neutral fat and the lipid ratios were calculated.⁶

Results and Comments. Table 1 gives the results of the analyses done on a series of rheumatoid arthritic patients receiving non-specific treatment (Group a), and on a second series receiving gold salt therapy (Group b). The total lipid values in the patients without gold salt therapy (Group a) and in the Group b patients before gold salt therapy varied from 306 to 611 mg. per 100 cc. of plasma. Plasma total cholesterol varied from 110 to 217 mg. per 100 cc., averaging 151; the phospholipid range was from 169 to 250. These figures and the other calculated lipid constituents and ratios are within the well-established limits for normal subjects and for patients with rheumatoid arthritis.^{3,13,18,19}

TABLE 1.—PLASMA LIPIDS IN RHEUMATOID ARTHRITIS DURING GOLD SALT THERAPY (RESULTS IN MG. PER 100 CC. OF PLASMA)

Subject	Age (yrs.)	Sex	Duration of disease (mos.)	Total lipid	Total fatty acid	Phospho-lipid fatty acid	Choles-terol ester fatty acid	Neutral fatty acid	Neutral fat	Cholesterol		Phospho-lipid phosphorus	Phospho-lipid	Total lipid/Total fatty acid	Total fatty acid/Neutral fat	Total fatty acid/Phospho-lipid	Phospho-lipid/Total cholest-erol
										Total	Ester						
Patients With Rheumatoid Arthritis (Group a)																	
1	54	M	4	414	260	135	62	63	60	135	92	8.25	203	1.59	4.34	1.28	1.50
2	62	F	7	460	299	141	72	86	82	158	107	8.45	211	1.54	3.64	1.41	1.32
3	33	M	12	537	394	121	66	107	101	145	99	7.29	182	1.36	3.90	2.16	1.25
4	41	M	12	348	207	130	64	13	12	139	95	7.80	195	1.68	17.20	1.06	1.40
5	24	M	30	398	243	136	85	22	21	187	127	8.18	205	1.64	11.50	1.18	1.10
6	33	M	36	463	309	143	70	96	91	153	104	8.55	214	1.50	3.4	1.44	1.40
7	43	F	84	352	212	154	62	137	93	9.20	230	1.66	..	0.92	1.67
8	56	F	96	611	408	148	92	168	159	202	137	8.93	223	1.50	2.56	1.82	1.10
9	40	M	120	306	196	130	50	16	15	110	75	7.80	195	1.56	13.00	1.00	1.77
10	38	F	228	416	283	134	60	87	83	132	90	8.05	201	1.47	3.40	1.41	1.52
Patients During Gold Salt Therapy (Group b)																	
1	54	M	6	430	318	133	52	133	126	113	77	8.00	200	1.35	2.52	1.59	1.77
				375	258	132	53	73	70	116	79	7.96	199	1.45	3.69	1.29	1.71
2	19	F	7	398	252	127	65	60	57	143	97	7.60	190	1.58	4.40	1.32	1.32
				458	310	158	66	86	82	146	99	9.53	238	1.47	3.60	1.30	1.63
				420	296	158	57	81	77	125	85	9.50	238	1.42	3.60	1.24	1.90
3	54	M	10	380	310	129	58	123	118	128	87	7.75	194	1.22	2.50	1.60	1.51
				481	370	140	52	178	169	114	78	8.43	211	1.30	2.19	1.75	1.85
				460	350	141	51	158	150	113	77	8.50	212	1.31	2.33	1.65	1.86
4	25	M	12	478	319	159	72	88	84	157	107	9.50	238	1.49	3.80	1.34	1.51
				—	—	—	—	—	—	—	—	—	—	—	—	—	—
				409	285	149	56	80	76	124	84	8.97	224	1.43	3.61	1.27	1.81
5	18	F	15	452	319	134	60	125	119	132	90	8.10	202	1.42	2.68	1.58	1.53
				489	346	160	65	121	115	142	97	9.68	241	1.41	3.00	1.43	1.70
				420	310	155	50	105	99	110	75	9.31	233	1.35	3.12	1.32	2.12
				433	290	158	67	65	62	147	100	9.54	238	1.49	4.68	1.22	1.62
6	28	F	18	408	201	157	92	48	..	202	137	9.41	235	2.03	..	0.86	1.16
				594	346	193	110	43	41	243	165	11.60	290	1.71	8.44	1.19	1.19
				548	301	172	109	33	31	240	162	9.55	239	1.82	9.72	1.25	1.00

TABLE 2.—PLASMA LIPIDS IN RHEUMATOID ARTHRITIS DURING PREGNANCY (RESULTS IN MG. PER 100 CC. OF PLASMA)

Subject	Age (yrs.)	Duration of arthritis (mos.)	Stage of gestation (wks.)	Total lipid	Total fatty acid	Patients With Rheumatoid Arthritis During Pregnancy (Group c)			Phospho-lipid phosphorus	Phospho-lipid	Total fatty acid/Neutral fat	Total fatty Phospho-lipid	Phospho-lipid/choles-terol		
						Choles-terol ester fatty acid	Neutral fatty acid	Neutral fat							
														Cholesterol	
						Total	Ester								
1	33	24	12	426	306	121	56	129	122	83	7.30	182	2.50	1.68	1.49
			28	550	425	167	58	200	190	128	87	10.05	251	2.24	1.69
2	35	60	6*	365	249	156	60	33	31	116	79	9.40	8.05	1.06	2.02
			28	613	397	172	97	128	122	213	145	10.35	259	3.25	1.53
3	28	28	12*	486	333	148	69	116	110	151	103	8.92	3.03	1.49	1.47
			32	604	412	165	87	160	152	192	136	9.15	248	2.70	1.66
4	39	48	16*	425	293	113	60	120	114	131	89	6.80	1.92	1.72	1.30
			32	389	273	148	54	71	67	117	80	8.90	222	4.08	1.23
			32	519	397	164	57	176	167	125	85	9.90	2.38	1.60	1.97

* Postpartum.

Gold salt therapy had startlingly little effect on partitioned plasma lipids, as shown in Table 1. Total lipids increased in 6 patients an average of 76 mg. per cc. and decreased in 5 an average of 35. Total cholesterol increased in 6 an average of 30 mg. per cc. and decreased in 5 an average of 23. Phospholipid values increased an average of 17 mg. per cc. in 6 patients and decreased an average of 21 in 5 patients. Calculated lipid constituents and ratios were unaltered during gold salt therapy. Apparent or real clinical improvement in patients during gold salt therapy was not correlated in any way with the individual plasma lipid changes noted in Table 1. It is not the purpose of this paper either to defend or abuse gold salt therapy in rheumatoid arthritis; but if it is a useful medicament in this disease, it can be seen from our results that the ameliorative effect is not brought about by a significant shift in the plasma lipids.

The changes in plasma lipids in rheumatoid arthritics during pregnancy (Group c) are shown in Table 2. Total lipids in 28 to 32 weeks of pregnancy had increased 26, 33, 42 and 50% in our cases. Schwarz *et al.*²¹ have found a variation of from 34 to 122% increase of total lipids at term, in their study of the development of lipemia during pregnancy, and point out in their paper that this increase is progressive and at a relatively constant rate. This would indicate that at term the total lipids in our patients would be within the range of the lipemia of pregnancy in normal subjects. The total cholesterol increase was 7, 10, 41 and 46% in our patients. This can be compared with Schwarz *et al.* who found a variation of 8 to 136% increase at term, and Boyd⁵ who reports a 25% average increase. These data indicate no unusual shift in total cholesterol in the pregnant arthritic. In our patients the phospholipid change was +7, 11, 16 and 45%, compared with Schwarz *et al.* who found a range of 20 to 160% increase at term, and Boyd's figure was a 25% average rise for this substance at term. Thus, the phospholipid shift was not unusual by actual measurement in pregnant rheumatoid arthritics. The calculated lipid substances and ratios shown in Table 2 show no unusual changes during pregnancy in rheumatoid arthritis as compared to those found during pregnancy in a normal subject.^{5,21,23}

While the ameliorative effect of pregnancy on rheumatoid arthritis is nearly as great as that of obstructive jaundice, it can be seen from our figures and those of others that the total lipid increases during pregnancy are minimal as compared to the profound lipid disturbance in obstructive jaundice.^{3,8,9,10,24,25} In this latter condition Freyberg³ found the total serum lipids are increased about 300%. The total cholesterol increased approximately 75%, with free cholesterol rising 3 to 4 times normal and the ester value remaining relatively unchanged. Phospholipids increased 200%.

If we compare these figures with those in the lipemia of pregnancy, the total cholesterol rise is seen to be only one-third that of jaundice with no change in the free/ester ratio. In this respect it differs greatly from the lipemia of jaundice, in which the hypercholesterolemia is almost entirely due to a great increase in free cholesterol with the esters

either remaining unchanged or below normal. Since the ameliorative effect of jaundice and pregnancy on rheumatoid arthritis is qualitatively the same, the difference in cholesterol metabolism in these two conditions cannot be invoked as the answer to the problem, and is probably unrelated to the favorable effect.

The total plasma lipid rise in pregnancy is roughly one-third that found in jaundice and the phospholipids rise only a fraction as much in pregnancy as in jaundice. From these facts it may be concluded that while the rise in plasma lipids is common to jaundice and pregnancy, and while both improve rheumatoid arthritis, the magnitude of the plasma lipid level beyond a certain point is not contributory. Some observers feel that the improvement noted with pregnancy does not occur as regularly or as completely as with obstructive jaundice. In two such widely divergent states as jaundice and pregnancy with their many physiologic facets, the common lipemia may be the ameliorative factor in both conditions, in one, or in neither state. Further, an intimate disturbance in lipid metabolism may exist in these two conditions which is not mirrored by the relatively crude measurement of plasma lipids. We hope to investigate this latter potentiality.

Summary. In patients with active rheumatoid arthritis, the total lipid, the total cholesterol and phospholipid plasma content is normal; the calculated lipids and lipid ratios are normal.

The plasma lipid constituents and ratios of rheumatoid arthritis studied during gold salt therapy showed little change during the administration of this medicament.

The lipemia of pregnancy in patients with active rheumatoid arthritis is qualitatively and quantitatively similar to that of normal pregnant subjects. From the data in this paper it can be concluded that the ameliorative effect of pregnancy on rheumatoid arthritis is not dependent upon a correction of a lipid deficiency nor a shift in lipid ratios which is different in any way from that found in normal subjects during pregnancy.

The differences and the similarities of the lipemias of jaundice and of pregnancy have been delineated, from which it is concluded that the remission produced in rheumatoid arthritis by these two conditions is not brought about by the magnitude of the lipemia nor the inherent differences in cholesterol metabolism. The common ameliorative effect remains unexplained.

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SICKLEMIA IN THE BLACK CARIB INDIAN*

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SICKLE cell anemia is undoubtedly "the most common primary blood dyscrasia in negro hospital patients" of the southern United States.† Moreover, the sickle cell trait is seen in a high percentage of apparently normal negroes in this country, the actual figures varying with the individual investigator from 5.3%¹⁶ to 14%¹² with an accepted average of about 7.5%. No studies of the sickling phenomenon appear to have been made on groups of negroes outside the United States.† The present report deals with a people who seem to have preserved wholly their integrity as a colored race, and among whom no cases of active sickle cell anemia have been identified in the hospital during the past 30-odd years.

Carib Indians at the San Juan village, 5 miles from the Tela Railroad Hospital at Tela, Honduras, were subjects of the present investigation. We were fortunate in receiving our introduction to them through one of their number who has attempted some detailed study of their

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† Since this manuscript was submitted for publication, an incidence of 15.5% sickling in physically fit, and 25% in sickly male West African soldiers has been observed by Evans (Evans, R. W.: *The Sickling Phenomenon in the Blood of West African Natives*, *Trans. Roy. Trop. Med. and Hyg.*, **37**, 281, 1944). *Abstr.—Biol. Abstr.*, **18**, 1171, 1944.

A second report (Mera, B.: *Preliminares des estudio de la meniscocitemia en Colombia*, *Bol. of San Panamericana*, **22**, 680, 1943; *Abstr.*, *Trop. Dis. Bull.*, **41**, 420, 1944) has just appeared stating that, of 489 negro school children examined in Puerto Tejada, Colombia, 46 (9.4%) proved positive for the presence of sickle cells. Of these, approximately 60% had sickle cell anemia, and the remaining 40%, the sickle cell trait.

origin. He recognizes 2 varieties of Caribs, the red and the black, and is sustained in this viewpoint by most authorities on the subject.^{1,6,8,15,25}

Any exhaustive discussion of the origin of these 2 groups of Caribs is far outside the scope of this report. As a matter of fact, very little ethnologic consideration seems to have been accorded them. Kennedy,¹⁵ Taylor,²⁵ Karsten,¹⁴ and Currier⁶ seem to be fairly well agreed, however, that the progenitors of these peoples came across the Atlantic from Africa, probably in sailboats of their own making, and apparently long before Columbus' epoch-making first voyage. They are still hardy sailors and are reputed to be the first peoples in the Western Hemisphere to use the sail as a means of power for propelling a boat. Taylor²⁵ describes the intermixture of the black Carib sailor and the Indian woman of the shores he invaded with the resultant development of the type to which the term red Carib has been given. Kennedy¹⁵ emphasizes the purity of the black Carib who apparently continued to hold himself apart from any peoples with whom he came in contact. It is upon the blood of the black Carib that the present studies were made.

Some knowledge of his customs and moral standards only serves to emphasize the manner in which he has kept himself apart from all other people with whom he has come in contact.^{14,15} The purity of his African ancestry is well demonstrated in the accompanying photograph which is an "at random" picture (Fig. 1). His features are characteristically negroid and without resemblance to other Indian tribes of North or South America. There is a heavy head of kinky, wooly, jet black hair. The skin varies in color from a chocolate brown to black, more commonly the latter. The forehead is wide; the eyes are keen with muddy yellowish (fatty) deposits in the scleræ; only occasionally are the cheek bones prominent; the nose is thick and flattened; the mouth is large, the lips thick, and the teeth well set and well preserved. Prognathism is not uncommon. Indeed, his resemblance to the African prototype is much more striking than that of his North American brother.

Material and Methods of Study. Of the 350 Carib Indians comprising the population of San Juan Village, Honduras, 300 were used as subjects. Of these, 133 were males, and 167 females. Their ages ranged from 4 months to 86 years, and are distributed numerically as follows:

TABLE 1.—AGE DISTRIBUTION OF SICKLING.

Years of age	No. of individuals	Individuals showing sickling	
		No.	%
0 to 4	42	5	11.9
5 to 10	42	7	16.7
10 to 19	76	4	5.2
20 to 29	47	5	10.6
30 to 39	46	2	4.4
40 to 49	20	0	
50 to 59	14	1	7.1
60 to 69	7	0	
70 to 79	2	0	
80 to 89	4	0	
Total	300	24	8.0

Blood smears were prepared on coverslips in the ordinary manner following puncture of the finger pad. They were then mounted on

microscopic slides and ringed with petrolatum to prevent drying. The slides were allowed to stand at room temperature (diurnal range from 72° to 87° F.) and were examined for sickling at approximately 2, 5, 18 and 24 hours after they were obtained. Resickling tests were carried out in a representative number, and in all instances in which there was doubt as to the change originally observed. Smears in which the cells failed to assume a characteristic form in this second trial were discarded as negative.

One hundred and thirty of the test subjects were questioned in regard to symptoms which might suggest that they had had acute episodes of sickle cell anemia. Specific questions were asked involving the recurrence, duration and severity of (a) joint and muscle pains, (b) "yellow eye-balls," (c) fever, and (d) abdominal pain. All persons with positive smears were interviewed at greater length.

Results. Twenty-four of the 300 individuals (8%), exhibited the sickling phenomenon in their red blood cells. The figures regarding age distribution are tabulated in Table 1, and those relating to sex and "sickling time," in Table 2.

TABLE 2.—TIME OF THE APPEARANCE OF SICKLING
Positive smears

Hours	Male		Female		Total
	No.	%	No.	%	
2	1	0.7	3	1.8	4
5	1	0.7	3	1.8	4
18	5	3.7	9	5.4	14
24	9	6.7	15	9.0	24

Sickling was observed in 9 of 133 males (6.7%), and in 15 of 167 females (9%). It was impossible to look for sickling immediately, but the low number of positives at the end of 2 hours and the statement of the director of the laboratories of the hospital that he had never seen sickling on ordinary blood smears would support the contention that the phenomenon is a rather latent trait among the group of peoples studied. The largest number (7) and the highest percentage (16.7) of positive smears occurred in the group between 5 and 10 years of age; in persons over 60 years old, the phenomenon was not observed; but neither of these variations is statistically significant.

Four of the 24 persons who shows sickled cells gave a history compatible with previous acute episodes of sickle cell anemia. However, in only 1 of these, a woman of 25 years, had icterus ever been noted. This had occurred but once at the age of 24, and was of such degree and character as to indicate definitely an attack of catarrhal jaundice rather than a crisis of the specific anemia. Histories were extremely difficult to evaluate in view of the prevalence of malaria and of intestinal parasites, either or both of which may produce disturbances symptomatically indistinguishable from the clinical syndrome found in sickle cell anemia.

Discussion. The present work was prompted by the following considerations: (1) The black Carib is a negro of relatively pure strain;

(2) sickling has not been studied in the tropics, nor indeed in negroes outside the United States; (3) the presence of sickle cell anemia in people not of the negro race has shown the necessity for careful evaluation of the statement that the disease arises from a hereditary racial trait; and (4) through 30-odd years, the records of one hospital in which Caribs are not infrequently patients fail to disclose a single case of identified sickle cell anemia.

1. The black Carib is a negro of relatively pure strain. We have adduced some evidence for this statement above; further pursuit of the subject can best be had by reference to Kennedy's article,¹⁵ the conclusions in which are based upon both the author's personal observations and the writings of his contemporary and antecedent historians.



FIG. 1.—Group of Carib children, San Juan Village, Tela, Honduras.

2. Negroes outside the United States have not been previously studied for the sickling trait. It seemed important to do this, as the past emphasis upon the racial limitation of the disease has precluded any recognition of the possible influence of climate, habits of eating and living, the admixture of white or other blood, the presence or absence of intercurrent or concurrent disease, and so forth. The results obtained tend to support the race-linked character of the condition, for sickling was observed in 8% of the individuals tested, which is in close accord for such a small series with the average figure (7.5%) obtained on large numbers of persons studied in this country. Moreover, the sickling trait appears to be most prominent in the age groups at which the onset of sickle cell anemia has been observed in this country, between birth and 10 years, with an average of 6.3 years as determined by the review of 214 cases.¹⁸

3. Sicklemia and sickle cell anemia apparently occur in peoples not of the negro race, though, as has often been pointed out, it is practically impossible to exclude negro admixture absolutely, *i. e.*, to the extent required by the geneticist. Sickle cell anemia has been described in 26 Caucasians of birth or parentage as noted below. These include

14 persons of Sicilian or souther Italian origin;^{2,3,9,10,11,19,20,21,22,29} an Arab boy;¹ 5 Greek children;^{5,13,26,27} 1 Mexican Indian in whom negro blood seems to have been excluded;²⁸ 1 Cuban in whom negro blood may have existed;²⁴ and 4 persons whose families have been established in the United States for several generations.^{4,17,23} When the cases are discarded in which there is doubt as to the diagnosis or the presence of negro blood in the immediate family, there remain 22 white patients with sickle cell anemia. Not only has active sickle cell anemia been noted in the white, but also the sickle cell trait has been observed among Indians who have had little opportunity for mixing with the negro. Killingsworth and Wallace¹⁶ found sickleemia in 1.2% of female Mexican Indians but none among the men of the same tribe. These facts place the entire concept of race linkage in jeopardy.

On the other hand, the present study carried out in a tropical environment and on a hitherto unstudied tribe of African origin has yielded results so closely in accord with those obtained on North American negroes as to support strongly the hereditary racial character of the disease, despite its sporadic appearance in individuals who fail to show negroid characteristics or family histories.

4. No cases of sickle cell anemia have been recognized during the past 30-odd years among "not infrequent" admissions of Carib Indians to a competently staffed hospital. That cases were not overlooked seems to be supported by the fact that but 4 of 130 persons interviewed afforded any semblance of a history suggestive of acute attacks of the disease, whereas, 24 of these individuals exhibited the sickling phenomenon. However, it is extremely easy to overlook the disease. Of 214 reported cases, a mistaken diagnosis was made in 97, or 45.3%, and operations were performed on the basis of such diagnoses in 21 instances.¹⁸ Further, the Carib is a very stoical individual, little giving to nursing his ills. It is well known that he almost never seeks outside medical care for malaria or intestinal disorders. It seems quite likely that by the same token he uses the tribal "doctor" or traditionally recommended herbs during his crises from sickle cell anemia.

On the other hand, do conditions in the tropics preclude the appearance of crises in people whose red blood cells carry the sickling trait? It seems unlikely that this question can be answered in the affirmative, as it has been shown by a number of investigators that the difference between sickleemia and sickle cell anemia is probably one of degree rather than one of kind. In both conditions the alterations occurring in the red cell are directly related to the oxygen tension and the hydrogen-ion concentration of the blood and tissues. There is little evidence to suggest that climatic conditions would seriously affect these factors.

Summary.—In wet, unstained preparations, the red blood cells of 24 of 300 Carib Indians of Honduras, Central America, showed the sickling phenomenon within a period of 24 hours. The sex and age incidence are noted. None of the individuals who showed sickling could be proved to have had active episodes of sickle cell anemia at any period of life. The significance of the findings is discussed, particularly in relation to the hereditary racial nature of the disease and

the sickling trait, and the environmental influences which may play a part in precipitating the crises.

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ARTERIOSCLEROTIC AND HYPERTENSIVE HEART DISEASE WITH RIGHT AXIS DEVIATION*

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THE purpose of this study was to determine the prognostic significance of right axis deviation among patients with arteriosclerotic and hypertensive heart disease.

Material. Twenty-six patients with definite historical, clinical or necropsy evidence of either arteriosclerotic or hypertensive heart disease were used as the basis for this study. These cases were selected from 259 instances of right axis deviation found in the review of the electrocardiograms of 10,500 patients, taken between the years 1936 to 1944 at the Veterans Administration Facility, Washington, D. C. No patients were included in the analysis who revealed either clinical

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or autopsy evidence of rheumatic or congenital heart disease or cor pulmonale.

Approximately 70% of all the cases of organic heart disease treated at this hospital during the years covered by this study were due to arteriosclerotic or hypertensive heart disease.¹¹ The majority of the patients predominantly male, were veterans of World War I with an average age, at this time, of slightly over 50 years. There were 741 cases of hypertensive heart disease with 236 deaths, and 595 instances of arteriosclerotic heart disease with 119 deaths; of the total 1336 patients, 355 (26.5%) died in the hospital. Among the arteriosclerotic heart disease group, 241 patients were considered to have presented the clinical picture of a recent coronary thrombosis with myocardial infarction.

The average age of the group of 24 white males and 2 white females with right axis deviation included in this study was 51.73 years, with an age range from 32 to 65 years. These 26 patients comprised 1.9% of the total group of arteriosclerotic and hypertensive heart disease. Twenty-two of these cases comprised 3.7% of the arteriosclerotic group, and the remaining 4 patients comprised 0.5% of those with hypertensive heart disease. A record of any previous elevation of blood pressure or a persistent blood pressure reading above 140 mm. Hg systolic or 90 mm. Hg diastolic was considered sufficient to diagnose the existence of arterial hypertension. In the 4 cases of hypertensive heart disease encountered in this series the systolic and diastolic readings were well above these arbitrary limits.

Twenty-four patients presented typical historical and clinical evidence, including characteristic electrocardiographic findings, of coronary thrombosis with myocardial infarction. On 19 occasions the electrocardiograms were rather typical of anterior wall infarction, and in 5 instances the electrocardiographic changes were characteristic of posterior wall infarction. In 2 cases the probable location of the myocardial damage could not be satisfactorily determined (Table 1).

Cardiac enlargement was found by roentgenographic studies in only 5 cases. Four of these cases died during hospitalization and the clinical impression of cardiac enlargement, especially left ventricular hypertrophy, was verified in the 3 cases that came to autopsy. In 21 of the 26 patients studied, the heart was considered to be within normal limits as to size. In appraising this finding, the transverse diameter of the heart, the cardio-thoracic ratio, general contour of the cardiac silhouette and the phase of respiration as seen on the roentgenograms, and the results of physical examinations were taken into consideration.

Arbitrary criteria for the establishment of right axis deviation was adopted and closely followed. These criteria were: (a) S-1 must be larger than R-1 and R-3 larger than R-2; (b) the QRS conduction time must be within normal limits, namely, not greater than 0.1 second; and (c) the largest QRS complex should be greater than 0.5 millivolt in amplitude. No grossly out-of-phase records were included in this study. All of the tracings considered as revealing right axis deviation showed an angle above 96 degrees, and in all but 3 of the electro-

cardiograms the angle was above 110 degrees as determined by the method of Dieuaide.⁴

Each patient at some one time revealed a right axis deviation. Nine individuals did not show a right axis deviation on the first electrocardiogram taken; in 8 instances the electrical axis was normal and in 1 a left axis deviation was present. Seventeen patients revealed a right axis deviation on the first available electrocardiogram, this finding persisting throughout the period of hospitalization in 14 instances; in 8 of these 14 patients there was no change whatsoever in the configuration of the QRS complexes while there were changes in the ST segments and T waves. In the entire group a right axis deviation was noted on only 1 tracing in 8 patients during a series of electrocardiograms; on 4 occasions the right axis deviation noted was obtained on the last tracing of a series.

TABLE 1.—ANALYSIS OF CLINICAL FINDINGS IN HYPERTENSIVE AND ARTERIOSCLEROTIC HEART DISEASE WITH RIGHT AXIS DEVIATION

Case No	Age	Sex	Clinical findings			Occlusion		Site of occlusion		Follow-up		
			Hypertension	Cardiac enlargement (Roentgen ray)	Myocardial infarction	Recent	Old	Anterior	Posterior	Alive	Dead	Duration
1	32	M	+	+	..	+	..	+	..	20 mos.
2	35	M	+	+	..	+	..	+	..	15 mos.
3*	38	M	+	+	+	..	+	+	..	+	..	1 mo.
4	42	M	+	+	+	+	..	26 mos.
5	44	M	+	+	..	+	..	+	..	41 mos.
6†	46	M	+	+	+	+	..	+	+	51 mos.
7	46	M	+	..	+	+	..	+	..	64 mos.
8	46	M	+	+	..	+	..	+	..	22 mos.
9	48	M	+	..	+	..	+	+	..	31 mos.
10	48	M	+	+	+	+	..	51 mos.
11	50	M	+	..	+	+	..	+	..	58 mos.
12	51	M	+	+	..	+	..	+	..	35 mos.
13	52	M	+	+	..	+	..	+	..	54 mos.
14	53	M	+	+	..	+	..	+	..	56 mos.
15	54	M	+	+	..	+	..	+	..	44 mos.
16	54	M	+	+	+	+	..	22 mos.
17	56	M	?	?	..	+	..	7 mos.
18	57	M	+	+	..	+	..	+	..	28 mos.
19	58	M	+	+	..	+	..	+	..	23 mos.
20†	61	F	?	?	?	+	..	23 mos.
21	61	M	+	..	+	+	..	+	..	79 mos.
22†	61	M	+	+	+	+	..	+	+	10 days
23	61	M	..	+	+	+	..	+	+	12 days
24†	62	M	+	+	+	+	+	..	+	23 days
25	64	M	+	+	..	+	..	+	..	64 mos.
26	65	F	+	+	..	+	+	1 day
Totals	26	24 M 2 F	4	5	24	19	5	19	5	21	5	
Av. age	51.73											2.5 yrs.
Range	32 to 65 yrs.											1 day to 79 mos.

* Cardiac aneurysm.

† Hemiplegia.

‡ Autopsy.

All of the patients have been traced (Table 1). Five (19.2%) of the group died and autopsy examinations were performed in 3 instances; 21 patients are still alive. To date, the average duration of life among all of the patients is 2.5 years, with an age range from 1 day to 79 months.

The 3 cases which came to autopsy revealed cardiac enlargement with definite ventricular hypertrophy and coronary thrombosis and infarction in each instance. The heart weights were 435, 533 and 637 gm. An advanced degree of arteriosclerosis of the coronary arteries was found in all of the cases. Recent coronary thrombosis occurred once in the main right posterior coronary artery and twice in the left anterior descending artery.

Discussion. Klainer⁷ was the first to attach any definite clinical prognostic significance to the findings of right axis deviation in hypertensive or arteriosclerotic heart disease. He concluded that the occurrence of right axis deviation with hypertensive or arteriosclerotic heart disease in the absence of rheumatic or congenital heart disease or cor pulmonale indicated a poor prognosis. Comeau and White³ and Nathanson⁹ have regarded right axis deviation in coronary heart disease as important in a negative sort of way. Comeau and White felt that the finding of right axis deviation is a strong though not conclusive evidence that the patient does not have coronary disease, and in such cases cor pulmonale particularly should be considered. Nathanson likewise concluded that the presence of coronary disease could be excluded on this feature alone, since most cases with primary right heart failure are associated with definite right ventricular preponderance. Nathanson reported that 2 out of 60 (3.3%) of the cases of coronary heart disease revealed right axis deviation. In a review of 200 cases showing right axis deviation, by Comeau and White,³ it was found that 7 out of 125 (5.6%) of the cases with organic heart disease were due to coronary heart disease; these 7 cases constituted 10.9% of all organic heart disease over 30 years of age with right axis deviation. In the present study, electrocardiographic evidence of right axis deviation was revealed during the course of coronary heart disease without arterial hypertension, in 22 out of 595 (3.7%) of the cases. This percentage figure cannot be considered as insignificant when one of the most common cardiac diseases affecting adult man is under consideration.

The prognosis in those cases of arteriosclerotic heart disease with myocardial infarction was much more favorable than those with hypertensive heart disease (Table 1). Twenty of the 21 surviving patients had no evidence of cardiac enlargement or arterial hypertension. Four of the 5 that died revealed definite roentgenographic evidence of cardiac enlargement, and 3 of the 5 had hypertension. These findings were somewhat in agreement with those tabulated by Klainer.⁷ In his series, 4 of the 5 known living patients revealed no evidence of hypertension or cardiac enlargement, and all 13 patients that were autopsied showed definite left ventricular preponderance. Among the 23 death cases reported by Klainer,⁷ 15 had hypertension and 18 presented clinical evidence of cardiac enlargement.

Bohning and Katz² found that the few cases of right axis shift in patients with myocardial infarction were associated with anterior wall infarction. A definite trend in this direction was noted in the present series, in which 19 patients presented electrocardiographic findings compatible with anterior wall infarction and 5 cases showed evidence interpreted as indicating posterior wall infarction. Nineteen of the 26 cases presented evidence of a recent coronary occlusion; 3 of these 19 showed T wave negativity in all 3 standard leads of the electrocardiogram. Barnes and Burchell¹ have reported that the majority of cases of negative T waves in all 3 leads associated with right axis deviation occurred in cases in which there had been a recent coronary occlusion.

TABLE 2.—INCIDENCE OF RIGHT AXIS DEVIATION IN HYPERTENSIVE AND ARTERIOSCLEROTIC HEART DISEASE

	No. of cases	% of total cases	Deaths	% of deaths
Hypertensive heart disease	737	99.5	233	31.6
Hypertensive heart disease with right axis deviation	4	0.5	3	75.0
Total hypertensive heart disease	741	100.0	236	31.8
Arteriosclerotic heart disease	573	96.3	117	20.4
Arteriosclerotic heart disease with right axis deviation	22	3.7	2	9.0
Total arteriosclerotic heart disease	595	100.0	119	20.0

One patient (Case 3) with an arterial hypertension and roentgenographic evidence of a left ventricular aneurysm revealed a right axis deviation that has persisted for 6 months. Eliaser and Konigsberg⁵ found that right axis deviation occurred frequently in cases of ventricular aneurysms. These authors were unable to establish any correlation between the location of the aneurysm in the left ventricle and the electrical axis produced on the electrocardiogram.

The outcome, to date, of the patients with myocardial infarction without evidence of arterial hypertension and showing right axis deviation was much more favorable than that found in the entire arteriosclerotic heart disease group (Table 2). On the other hand, the small group of patients with hypertensive heart disease and right axis deviation revealed a more unfavorable prognosis than the entire group with hypertensive heart disease. There were 117 deaths (20.4%) among the 573 cases of arteriosclerotic heart disease, without evidence of either hypertension or right axis deviation; while only 2 (9%) of 22 similar patients with right axis deviation died. In the hypertensive heart disease group, 3 out of 4 patients with right axis deviation died; 233 (31.6%) of 737 cases without right axis deviation died during hospitalization.

The mechanisms involved in the cases with right axis deviation is not clear, and no adequate explanation could be made by an analysis of the 26 cases now being reported. Inasmuch as most of the patients revealed no evidence of cardiac enlargement or recognizable intraventricular conduction defects, other possible causes of the right axis

deviation must be offered. Pardee¹⁰ and Hermann and Wilson⁶ showed that the position of the heart in such instances may be an important factor resulting in a right axis deviation. Meek and Wilson⁸ concluded that the rotation of the heart, while in its normal position, to the right on the anterior-posterior axis or to the left on the longitudinal axis of the heart will result in a right axis deviation in the electrocardiogram.

No close relationship should necessarily exist between the electrical R-axis and cardiac lesions known to exist beyond the main branches of the bundle of His.¹² This may be a factor in the finding of the right axis deviation in a large number of the cases reported in this series. Seventeen tracings showed a right axis deviation on the first tracing obtained and 14 of these showed a right axis deviation throughout the study. In these instances the right axis may have been present for sometime, and even before the existence of the cardiac condition. In a series of 200 unselected cases of right axis deviation,³ 32.6% of all the cases above 30 years of age were thought to be in normal hearts. The right axis deviation present in a majority of the present series may have been coincidental findings in the clinical picture and actually indicated little if any involvement of the main branches of the bundle of His.

Conclusions. In the study of the data from a series of 26 cases of arteriosclerotic or hypertensive heart disease showing right axis deviation on the electrocardiogram, and without clinical evidence of valvular or congenital heart disease or cor pulmonale, the following conclusions were drawn:

1. Right axis deviation was not a common occurrence in the presence of arteriosclerotic heart disease, having been found in 22 (3.6%) of 595 arteriosclerotic heart disease cases.

2. Right axis deviation, when there is no cardiac enlargement, does not preclude a poor prognosis in arteriosclerotic heart disease. In this group of cases the prognosis was actually strikingly better than the entire group of arteriosclerotic patients encountered under similar hospital conditions.

3. In a small series of patients (only 4) with hypertensive heart disease the prognosis was unfavorable and definitely more serious than among the entire group of patients with hypertensive heart disease.

4. Right axis deviation, in patients with myocardial infarction, was more common in anterior than posterior wall infarctions.

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THE INFLUENCE OF PITUITRIN AND EPINEPHRINE ON THE ACTION OF INSULIN ON BLOOD SUGAR

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I. Pituitrin and Insulin. Textbooks on pharmacology, physiology and medicine accept the statement that pituitrin decidedly counteracts the action of insulin on blood sugar. Characteristic studies upholding this statement are exemplified by the following 2 articles. In 1923 Burn³ observed that subcutaneous injections of extract of the posterior lobe of the pituitary gland, given simultaneously with subcutaneous injections of insulin, decreased or abolished the fall of blood sugar produced by the latter. He also found that pituitrin removed the symptoms of hypoglycemic convulsions, causing a rapid elevation of the blood sugar. He concluded from these studies that pituitrin is an antagonist of insulin. Davidoff and Cushing⁴ confirmed the findings of Burn. In 3 patients suffering from acromegalic diabetes, who had been shown to respond normally to insulin, 20 units of insulin combined with 1 cc. of pituitrin were injected. The expected fall in blood sugar at the end of a 2-hour period did not occur. Geiling *et al.*⁵ found the same to be true in dogs when insulin was given intravenously.

While the work reported here was in progress, an important contribution was made by Griffiths.⁷ He showed that in rabbits posterior pituitary extracts invariably inhibited the hypoglycemia due to subcutaneous injections of insulin; but in many of the rabbits no antagonism to intravenously administered insulin was found. In other rabbits, however, the antagonism to intravenous insulin was well defined. He suggested that the antagonism between subcutaneously injected insulin and posterior lobe extracts is mainly due to a decreasing rate of absorption, probably as the result of the vasoconstrictor action of the pressor substance. Young¹¹ had previously made a similar postulation.

A review of the literature reveals that no work has been done on the influence of pituitrin on the blood sugar curve of diabetic patients receiving dextrose. We decided to do this work in the hope that our knowledge of the relationship between insulin and pituitrin would be clarified.

Before proceeding with the description of the experiments, it is important to note the following. It has been shown by us¹⁰ that if equivalent amounts of dextrose and starch are given 2 days apart to a diabetic patient, the curves for the blood sugar contents of the blood

and urine will be identical. It is reasonable to assume that the same will hold true if equal quantities of dextrose are given 2 days apart. Consequently, if on one of the days of experimentation one new factor is introduced, such as the giving of pituitrin, any changes that may occur in the blood sugar curve must be considered significant.

EXPERIMENT 1. Diabetic Patients Receiving Dextrose and Dextrose Plus Pituitrin. Method of Procedure: Experiments were performed on 10 diabetic patients. To each of them, early in the morning after a fast of 14 hours, 70 gm. of dextrose were given orally in sufficient aqueous solution to constitute a total volume of 500 cc. Specimens of venous blood were taken at the fasting level immediately before ingestion, and 1 hour and 2 hours after the ingestion of the dextrose. The sugar content of the blood was determined by the Folin-Wu method. Urine was collected 1 hour and 2 hours after ingestion of dextrose, and its sugar content determined by the Benedict method. Two days later an identical procedure was carried out with the following addition: Immediately before ingestion of the dextrose, also 1 hour later, 1 cc. of pituitrin* was injected subcutaneously.

Patients receiving protamine-zinc insulin abstained from it for 3 days immediately preceding the study, while those taking unmodified insulin abstained for 24 hours. No insulin was taken in the 2-day interval between tests. As will be seen subsequently in this experiment and in all the others that follow in which the same procedure was used, the fasting values on the 2 days of experimentation are identical. It may be assumed, therefore, that by this method the influence of exogenous insulin, previously administered, is completely eliminated.

TABLE 1.—BLOOD SUGAR IN DIABETIC PATIENTS (a) AFTER INGESTION OF DEXTROSE, AND (b) AFTER INGESTION OF DEXTROSE PLUS PITUITRIN

(1) 70 gm. of dextrose in 500 cc. aqueous solution.

(2) 1 cc. of pituitrin (10 International Units) subcutaneously, immediately before ingestion of dextrose and 1 cc. 1 hour later.

Case No.	Blood sugar (mg./100 cc.)						Urine (0 to 2 hours post cibum)					
	Fasting level		One hour post cibum		Two hours post cibum		Volume (cc.)		Sugar (%)		Sugar (gm.)	
	Dext.	Dext. + Pit.	Dext.	Dext. + Pit.	Dext.	Dext. + Pit.	Dext.	Dext. + Pit.	Dext.	Dext. + Pit.	Dext.	Dext. + Pit.
1	331	322	605	555	588	540	430	285	3.8	4.6	16.3	13.1
2	317	328	488	476	548	506	225	250	5.0	3.7	11.3	9.3
3	247	250	526	520	526	500	423	310	4.2	4.1	17.8	12.7
4	292	282	414	413	414	476	322	310	4.0	4.8	12.9	14.9
5	140	118	256	330	178	392	210	140	1.3	4.2	2.7	5.9
6	171	178	314	258	374	..	164	108	5.0	3.0	8.2	3.2
7	294	260	440	413	408	513	350	285	5.0	4.7	17.5	13.4
8	219	204	404	435	388	409	332	275	4.6	4.6	15.3	12.7
9	181	172	298	272	317	334	242	142	4.5	4.1	10.9	5.8
10	163	170	308	312	308	388	615	298	1.5	2.5	9.2	7.5
Average	235	228	405	398	406	451	331	240	3.9	4.0	12.2	9.8

In Table 1 is shown the effect of pituitrin in diabetic patients on (1) the concentration of dextrose in the blood, (2) volume of urine, (3) concentration of dextrose in the urine, and (4) amount of dextrose in

* The pituitrin used was the Infundin of Burroughs, Wellcome & Co. Each cc. contains 10 International Units. The same preparation was used in all the other experiments which will be described below.

the urine after ingestion of 70 gm. of dextrose. It is evident that the blood sugar after ingestion of dextrose is not significantly greater when dextrose alone is given than when dextrose plus pituitrin are administered. The volume of urine when pituitrin and dextrose are given is significantly less than when dextrose alone is given, but not markedly so. The diuretic action of dextrose overcomes, to a great degree, the powerful antidiuretic action of pituitrin. The concentration of dextrose in the urine and the glycosuria are not significantly different. It is justifiable to conclude that pituitrin does not have any influence on the concentration of dextrose in the blood nor on the amount of dextrose in the urine in diabetic patients after the ingestion of dextrose. Apparently, pituitrin does not have any influence on the action of endogenous insulin.

EXPERIMENT 2. Diabetic Patients Receiving Dextrose Plus Insulin (Subcutaneously) and Dextrose Plus Insulin (Subcutaneously) Plus Pituitrin. In view of the findings made by Burn³ and others, it was thought of interest to study the effect of pituitrin on the action of insulin given subcutaneously to diabetic patients receiving dextrose. Experiments were performed on 7 diabetic patients. The method of procedure was identical with that of Exp. 1, with the following modifications: Twenty units of unmodified U 40 insulin were given subcutaneously on the 1st day of experimentation $\frac{1}{2}$ hour before the ingestion of dextrose. Two days later, insulin was again given in the same manner and, in addition, 1 cc. of pituitrin was injected subcutaneously immediately before the ingestion of dextrose and 1 hour later. The pituitrin and insulin were injected in different sites.

TABLE 2.—BLOOD SUGAR IN DIABETIC PATIENTS (a) AFTER INGESTION OF DEXTROSE PLUS INSULIN SUBCUTANEOUSLY, AND (b) AFTER INGESTION OF DEXTROSE PLUS INSULIN SUBCUTANEOUSLY PLUS PITUITRIN

- (1) 70 gm. of dextrose in 500 cc. aqueous solution.
- (2) 20 units of insulin subcutaneously $\frac{1}{2}$ hour before ingestion of dextrose.
- (3) 1 cc. of pituitrin (10 International Units) immediately before ingestion of dextrose, and 1 cc. 1 hour later.

Case No.	Blood sugar (mg./100 cc.)						Urine (0 to 2 hours post cibum)					
	Fasting level		One hour post cibum		Two hours post cibum		Volume (cc.)		Sugar (%)		Sugar (gm.)	
	Dext.		Dext.		Dext.		Dext.		Dext.		Dext.	
	Dext. + Ins. + Pit.	+ Ins.	Dext. + Ins. + Pit.	+ Ins.	Dext. + Ins. + Pit.	+ Ins.	Dext. + Ins. + Pit.	+ Ins.	Dext. + Ins. + Pit.	+ Ins.	Dext. + Ins. + Pit.	+ Ins.
1	294	280	358	400	342	460	160	284	5.0	6.0	8.0	17.0
2	288	308	151	370	65	364	42	170	1.0	3.8	0.4	6.5
3	252	284	308	440	377	470	109	248	4.2	4.6	4.6	11.4
4	200	181	189	204	131	210	340	126	0.0	1.0	0.0	1.3
5	131	118	106	113	70	86	60	62	0.0	0.0	0.0	0.0
6	163	167	205	286	118	340	368	187	0.0	0.8	0.0	1.5
7	220	236	367	318	262	421	270	350	3.3	2.9	8.9	10.2
Average	221	225	241	304	195	336	193	204	1.9	2.7	3.1	5.4

In Table 2 is shown the effect of pituitrin in diabetic patients receiving insulin subcutaneously on (1) concentration of dextrose in the blood, (2) volume of urine, (3) concentration of dextrose in the urine, and (4) amount of dextrose in the urine after the ingestion of dextrose. Allowing for the irregularities encountered, the blood sugar is greater

after the ingestion of dextrose plus subcutaneous insulin plus pituitrin, than when dextrose plus subcutaneous insulin alone are administered. This is especially evident 2 hours after ingestion of the dextrose. The same holds true for the amount of dextrose in the urine. These findings confirm the conclusions of Burn and others that pituitrin counteracts the action of insulin given subcutaneously.

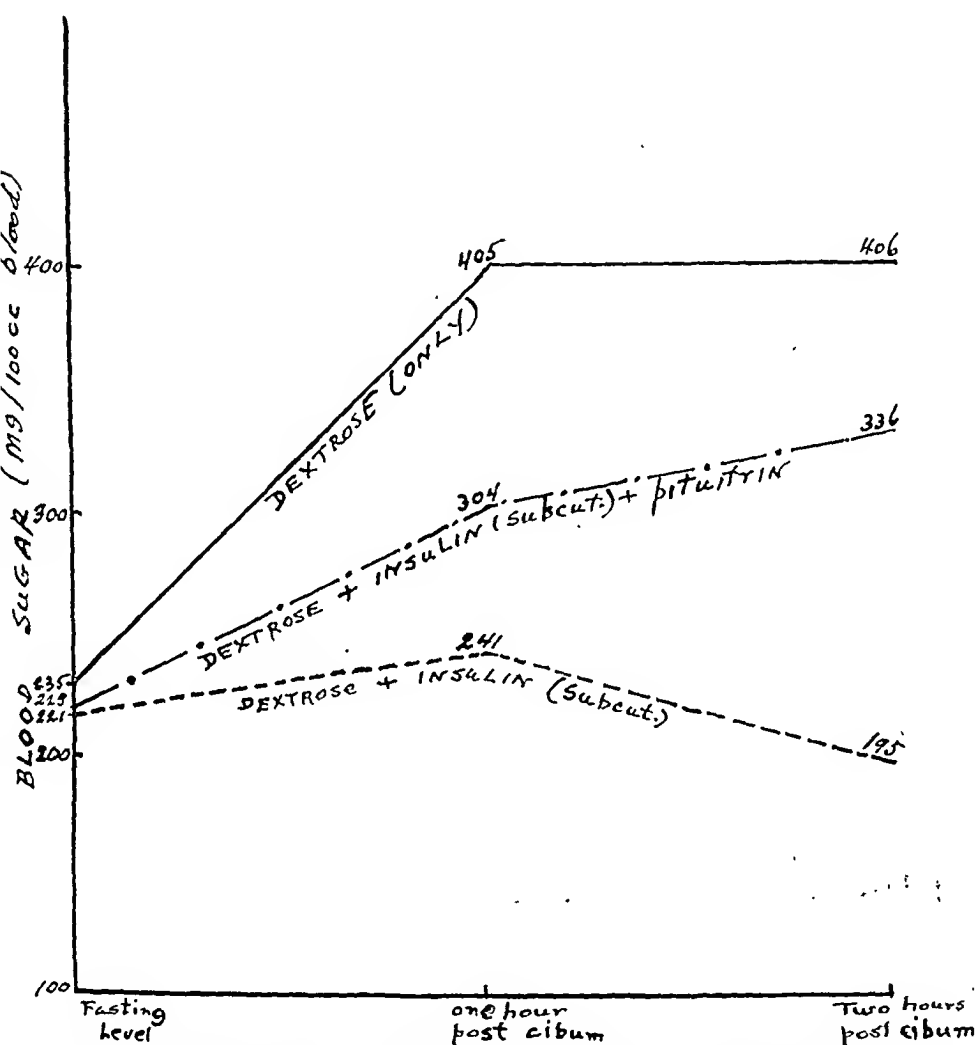


CHART 1.—Blood sugar curves in diabetic patients (1) after dextrose, (2) after dextrose plus insulin subcutaneously, and (3) after dextrose plus insulin subcutaneously plus pituitrin.

It is of interest to note to what degree pituitrin antagonizes the action of insulin given subcutaneously. The 10 diabetic patients of Exp. 1 (who received no insulin and no pituitrin on the 1st day of experimentation) have an average fasting blood sugar of 235 mg. per 100 cc. blood as compared to a fasting value of 221 in those of Exp. 2. These 2 groups may be considered identical as far as severity is concerned. Blood sugar curves, when the same amount of dextrose is

given to the 2 groups, would be practically identical. In Chart 1 are recorded the blood sugar curves where the following was given: Curve 1, 70 gm. of dextrose only; curve 2, 70 gm. dextrose plus subcutaneous insulin; curve 3, 70 gm. dextrose plus subcutaneous insulin plus pituitrin. It will be observed that whereas the blood sugar rises to 406 two hours post cibum when dextrose alone is given, it rises to only 336 when dextrose plus insulin plus pituitrin are administered. The conclusion is that, in the doses used, pituitrin only partially neutralizes the action of insulin on blood sugar.

Analysis of the results of Exp. 1 and 2 shows that pituitrin affects endogenous insulin and subcutaneously injected exogenous insulin differently. In Exp. 1, pituitrin apparently does not affect the action of endogenous insulin; in Exp. 2, however, the action of exogenous insulin is apparently counteracted. This led to the assumption that the mode of administration of insulin was significant. Accordingly, it was decided to study the action of pituitrin when insulin was given intravenously.

EXPERIMENT 3. *Diabetic Patients Receiving Dextrose Plus Insulin Intravenously and Dextrose Plus Insulin Intravenously Plus Pituitrin.* Method of Procedure: Experiments were performed on 8 diabetic patients. The method of procedure was identical with that of Exp. 1, with the following modifications. Fifteen units of unmodified insulin were given intravenously, immediately before ingestion of dextrose. Two days later, insulin was again given in the same manner and, in addition, 1 cc. pituitrin was given subcutaneously, immediately before the ingestion of the dextrose and 1 hour later.

TABLE 3.—BLOOD SUGAR IN DIABETIC PATIENTS (a) AFTER INGESTION OF DEXTROSE PLUS INSULIN INTRAVENOUSLY, AND (b) AFTER INGESTION OF DEXTROSE PLUS INSULIN INTRAVENOUSLY PLUS PITUITRIN

- (1) 70 gm. of dextrose in 500 cc. aqueous solution.
- (2) 15 units of insulin intravenously immediately before ingestion of dextrose.
- (3) 1 cc. of pituitrin (10 International Units) immediately before ingestion of dextrose, and 1 cc. 1 hour later.

Case No.	Blood sugar (mg./100 cc.)						Urine (0 to 2 hours post cibum)					
	Fasting level		One hour post cibum		Two hours post cibum		Volume (cc.)		Sugar (%)		Sugar (gm.)	
	Dext.		Dext.		Dext.		Dext.		Dext.		Dext.	
	Dext. + Ins. + Pit.	+ Ins.	Dext. + Ins. + Pit.	+ Ins.	Dext. + Ins. + Pit.	+ Ins.	Dext. + Ins. + Pit.	+ Ins.	Dext. + Ins. + Pit.	+ Ins.	Dext. + Ins. + Pit.	+ Ins.
1	165	184	98	87	128	111	165	80	0	0	0	0
2	240	226	180	144	109	116	128	95	0.8	0	1.0	0
3	388	345	320	206	328	180	95	90	2.5	2.0	2.4	1.8
4	336	318	156	265	280	342	25	45	0.5	1.4	0.1	0.6
5	248	256	197	195	100	166	60	55	0.5	1.7	0.3	0.9
6	234	256	97	129	152	171	58	52	0	0	0	0
7	270	267	140	125	129	188	44	57	0.8	1.3	0.4	0.7
8	276	261	111	212	252	276	61	0	2.0	0.0	1.2	0
Average	270	264	162	170	185	194	80	59	0.9	0.8	0.7	0.5

In Table 3 is shown the effect of pituitrin in diabetic patients receiving insulin intravenously on (1) concentration of dextrose in the blood, (2) volume of urine, (3) concentration of dextrose in the urine, and (4) amount of dextrose in the urine after the ingestion of dextrose. Analysis of the results reveals that pituitrin in no way affects the action of

insulin given intravenously on blood sugar and glycosuria in diabetic patients receiving dextrose. These findings are in striking contrast to those in Exp. 2, where insulin was given subcutaneously. They are in agreement with those made by Griffiths.

It has been shown by Goadby and Richardson that insulin, injected intravenously in rabbits, remains in the circulation in detectable amounts for about 90 minutes. In our patients, therefore, pituitrin was given the opportunity to counteract the action of insulin given intravenously. Such action, however, did not occur. We must conclude, therefore, that pituitrin does not antagonize the action of insulin.

By what means then does pituitrin counteract the action of insulin given subcutaneously? The first possibility that suggests itself is that pituitrin, by virtue of its vasoconstrictor action, retards the absorption of insulin from subcutaneous tissues. This is the theory entertained by Griffiths⁷ and Young.¹¹ Indeed, this action of pituitrin has been utilized in "Deposulin," which is a mixture of insulin and pituitrin. It is claimed by Taeger and Danish,⁹ Holland and Weger,⁸ and Baudouin *et al.*¹ that the action of insulin is definitely prolonged as a result of this procedure. To avoid this local action of pituitrin, the insulin and pituitrin in our experiments were given subcutaneously in different sites.

Does pituitrin retard the absorption of insulin under these circumstances? This question can be answered in part by the following experiment. Phenolsulphonphthalein, injected subcutaneously, is absorbed into the circulation, excreted by the kidney, and its amount in the urine can be measured with exactness. Any retardation of absorption will manifest itself by a decrease in excretion by the kidneys. The following experiment was accordingly performed.

Method of Procedure: Experiments were performed on 6 normal adults. Each was injected subcutaneously with 1 cc. of solution containing 6 mg. of phenolsulphonphthalein. Each patient drank 500 cc. of water at the time of injection and 250 cc. 1 hour later. Urine was collected 1 hour and 2 hours after the injection of phenolsulphonphthalein. Two days later an identical procedure was carried out. In addition, 1 cc. of pituitrin was injected subcutaneously 5 minutes before phenolsulphonphthalein was injected, and 1 cc. 1 hour later. The pituitrin and phenolsulphonphthalein were injected in different sites. The phenolsulphonphthalein content of the urine was determined in the usual manner. The large quantity of water was given to insure an adequate excretion of urine, since pituitrin is a powerful antidiuretic.

In Table 4 are recorded the volumes of urine and amounts of phenolsulphonphthalein excreted during the 1st and 2nd hours after the injection of the phenolsulphonphthalein. The volume of urine is, of course, markedly less when pituitrin is injected. The amounts of phenolsulphonphthalein excreted, however, are not significantly greater when phenolsulphonphthalein alone is injected than when phenolsulphonphthalein and pituitrin are injected. The conclusion is clear that pituitrin does not retard the absorption of phenolsulphonphthalein from the subcutaneous tissues. An important consideration is the fact

that phenolsulphonphthalein has a very low molecular weight as compared with insulin, which is a protein. The absorption rate of the latter is much less than that of phenolsulphonphthalein. In view of the fact that pituitrin does not retard the absorption of phenolsulphonphthalein from the subcutaneous tissues, it is doubtful whether it appreciably retards the absorption of insulin; certainly not to a degree to account for the findings made in Exp. 2. It must be concluded, therefore, that the manner in which pituitrin counteracts the action of insulin given subcutaneously cannot, in the present state of our knowledge, be explained and awaits further research for its elucidation.

TABLE 4.—EXCRETION OF PHENOLSULFONPHTHALEIN, INJECTED SUBCUTANEOUSLY IN NORMAL INDIVIDUALS, IN URINE, WITH AND WITHOUT SIMULTANEOUS SUBCUTANEOUS INJECTION OF PITUITRIN

Pituitrin—1 cc. (10 International Units) injected 5 minutes before injection of phenolsulfonphthalein, and 1 cc. injected 1 hour later.

Water—500 cc. ingested immediately before injection of phenolsulfonphthalein, and 250 cc. 1 hour later.

Phenolsulfonphthalein—the amount injected was 1 cc. containing 6 mg. of the dye.

Case No.	Volume of urine (cc.)						P.S.P. excretion (%)					
	First hour		Second hour		Total 2 hours		First hour		Second hour		Total 2 hours	
	P.S.P.	P.S.P. + Pit.	P.S.P.	P.S.P. + Pit.	P.S.P.	P.S.P. + Pit.	P.S.P.	P.S.P. + Pit.	P.S.P.	P.S.P. + Pit.	P.S.P.	P.S.P. + Pit.
1	135	60	385	62	520	122	38	26	23	21	61	47
2	133	80	610	60	743	140	17	27	32	14	49	41
3	340	55	376	45	716	100	14	43	18	22	32	65
4	237	57	550	30	787	87	32	31	23	17	55	48
5	185	60	703	50	888	110	22	25	26	16	48	41
6	190	28	380	30	570	58	49	43	16	2	65	45
Average	203	57	504	46	706	103	28.7	32.5	23	15.3	51.7	47.8

It is of interest to discuss the clinical value of these findings. The experiments reported here revealed an appreciable, but not striking, antagonism of pituitrin to the action of subcutaneous insulin on blood sugar. The dose of pituitrin used was 20 units during the 2-hour period of experimentation. The dose of insulin was comparatively small, only 15 units. The dose of pituitrin used here is far in excess of that employed clinically. This action of pituitrin is, therefore, chiefly of interest physiologically. It need not be taken into consideration in determining the dose of insulin in diabetic patients where pituitrin is being administered simultaneously.

II. Epinephrine and Insulin.—The literature on the action of epinephrine on blood sugar is enormous and need not be reviewed here. It is sufficient to state that it has been amply proved that epinephrine is an antagonist of insulin, as far as blood sugar is concerned. The remarkable difference in the action of pituitrin on insulin, given subcutaneously and intravenously, made us speculate as to whether such a difference in action also exists with epinephrine. The literature is replete with experiments on the action of epinephrine on insulin given subcutaneously. The only work on intravenously injected insulin is by Berg, Gross, McAfee, and Zucker² who found that epinephrine does not influence the blood sugar lowering effect of intravenously injected insulin in normal and depancreatized dogs. We decided to investigate this subject in human diabetics.

EXPERIMENT 5. *Diabetic Patients Receiving Dextrose Plus Subcutaneous Insulin and Dextrose Plus Subcutaneous Insulin Plus Epinephrine.* Method of Procedure: Experiments were performed on 6 diabetic patients. Each of them was injected subcutaneously with 20 units of unmodified insulin early in the morning after a fast of 14 hours. Each was given, orally, 70 gm. of dextrose $\frac{1}{2}$ hour later in

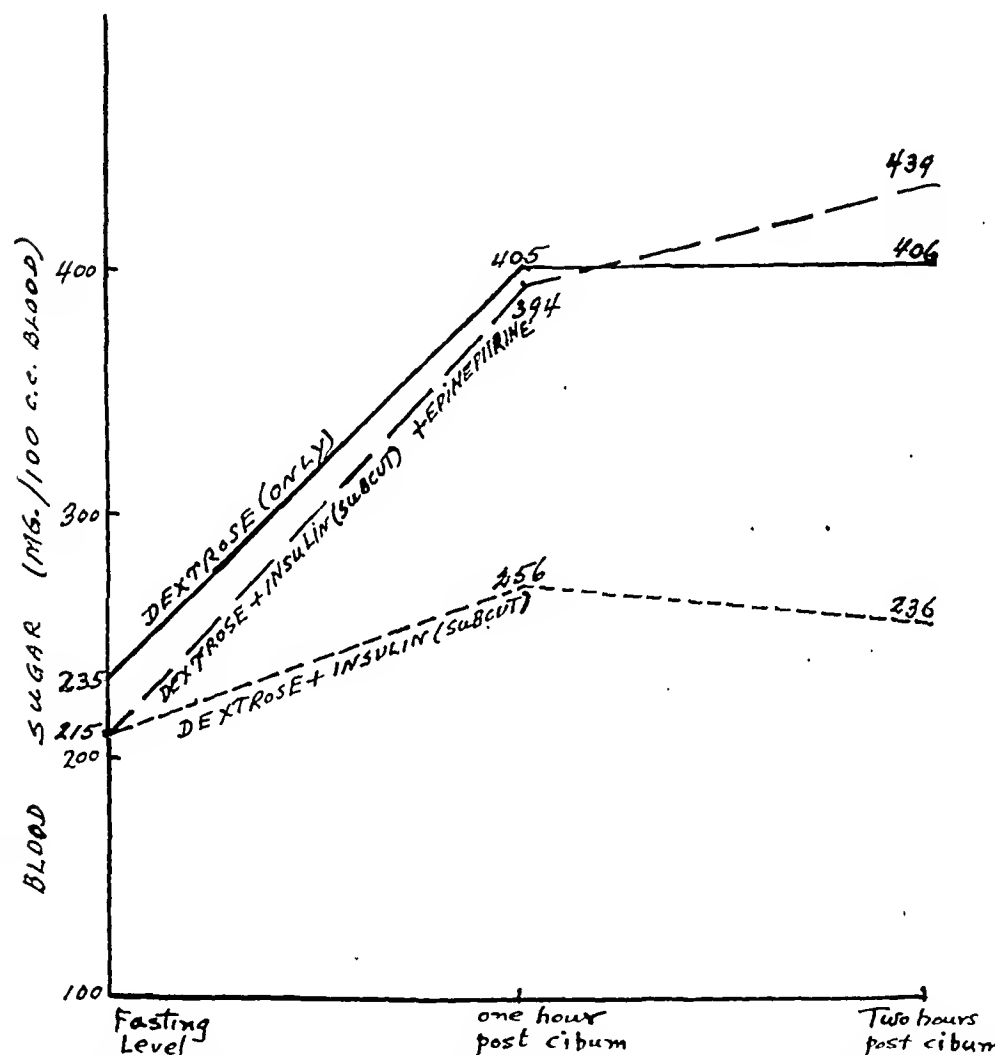


CHART 2.—Blood sugar curves in diabetic patients (1) after dextrose, (2) after dextrose plus insulin subcutaneously, and (3) after dextrose plus insulin subcutaneously plus epinephrine.

sufficient aqueous solution to constitute a total volume of 500 cc. Specimens of blood were taken at the fasting level, and 1 hour and 2 hours after ingestion of dextrose. The sugar content of the blood was determined by the Folin-Wu method. Two days later an identical procedure was carried out, with the following modifications. Ten minutes before the ingestion of the dextrose, also 75 minutes later, 10

minims of epinephrine hydrochloride (1 to 1000) were injected subcutaneously. Patients receiving protamine zinc insulin abstained from it for 3 days immediately preceding the study, while those taking unmodified insulin abstained 24 hours. No insulin was taken in the 2-day interval between tests.

In Chart 2 is shown the effect of epinephrine on blood sugar in diabetic patients receiving dextrose and subcutaneous insulin. The blood sugar values in Curve 2 are the averages (6 cases) when dextrose and subcutaneous insulin are given, while those in Curve 3 are the averages when dextrose plus subcutaneous insulin plus epinephrine are administered. It is evident that the blood sugar, after ingestion of dextrose plus subcutaneous insulin plus epinephrine, is markedly greater than when dextrose plus subcutaneous insulin alone are administered.

It was stated above that pituitrin in the doses used counteracted the action of insulin only partially. It is of interest to note to what degree epinephrine antagonizes the action of insulin. The 10 diabetic patients of Exp. 1 (who received no insulin and no pituitrin on the 1st day of experimentation) have an average fasting blood sugar of 235 mg. per 100 cc. blood, as compared to a fasting value of 215 in those of Exp. 5. These 2 groups can be considered almost identical as far as severity is concerned. Blood sugar curves, when the same amounts of dextrose are given, would be practically identical. In Chart 2 are recorded the blood sugar curves when the following are given: Curve 1, dextrose only; Curve 2, dextrose plus subcutaneous insulin; Curve 3, dextrose plus subcutaneous insulin plus epinephrine. It will be observed that Curves 1 and 3 are practically identical. The conclusion is that, in the doses given, epinephrine completely neutralizes the action of insulin on blood sugar.

EXPERIMENT 6. Diabetic Patients Receiving Dextrose Plus Intravenous Insulin and Dextrose Plus Intravenous Insulin Plus Subcutaneous Epinephrine. It was found above that pituitrin in no way influences the action of insulin, given intravenously, on blood sugar. It was considered of interest to make a similar study of the action of epinephrine on insulin given intravenously.

Method of Procedure: The method of procedure was identical with that of Exp. 5, with the following modifications: (1) Fifteen units of unmodified insulin were injected intravenously immediately before the ingestion of dextrose. (2) Ten minutes of epinephrine hydrochloride (1 to 1000) were injected subcutaneously immediately before the ingestion of dextrose and a similar dose 1 hour later.

In Table 5 is shown the effect of epinephrine on blood sugar in diabetic patients receiving dextrose and intravenous insulin. It is evident that the blood sugar, after injection of dextrose plus intravenous insulin plus subcutaneous epinephrine, is markedly greater than when dextrose and intravenous insulin alone are given. The conclusion is that epinephrine decidedly antagonizes the action of intravenous insulin on blood sugar; and to a degree almost equal to that of epinephrine on subcutaneously injected insulin.

TABLE 5.—BLOOD SUGAR IN DIABETIC PATIENTS (a) AFTER INGESTION OF DEXTROSE PLUS INSULIN INTRAVENOUSLY, AND (b) AFTER INGESTION OF DEXTROSE PLUS INSULIN INTRAVENOUSLY PLUS EPINEPHRINE

- (1) 70 gm. of dextrose in 500 cc. aqueous solution.
 (2) 15 units of insulin, intravenously, immediately before ingestion of dextrose.
 (3) 10 minims of epinephrine hydrochloride (1 to 1000) 10 minutes before ingestion of dextrose, and 10 minims 1 hour later.

Case No.	Blood sugar					
	Fasting level		One hour post cibum		Two hours post cibum	
	Dext. + Ins.	Dext. + Ins. + Epineph.	Dext. + Ins.	Dext. + Ins. + Epineph.	Dext. + Ins.	Dext. + Ins. + Epineph.
1 . . .	272	320	288	514	308	482
2 . . .	320	374	149	380	127	460
3 . . .	203	154	213	300	226	395
4 . . .	353	280	218	385	154	423
5 . . .	337	326	500	469	500	517
Average .	297	291	274	410	263	455

This action of epinephrine on intravenously injected insulin is in marked contrast to that of pituitrin which does not in the slightest, influence the action of intravenously injected insulin.

Summary and Conclusions.—1. Evidence is presented to negate the generally accepted opinion that pituitrin counteracts the action of insulin.

2. Experiments reported in this paper reveal the following: (a) Pituitrin does not influence the blood sugar curve of diabetic patients receiving dextrose. (b) Pituitrin definitely counteracts the action of insulin, given subcutaneously, on the blood sugar curve of diabetic patients receiving dextrose. In the doses used, the neutralization of the action of insulin on blood sugar was only partial. (c) Pituitrin does not, in the slightest, influence the action of insulin, given intravenously, on the blood sugar curve of diabetic patients receiving dextrose.

3. The fundamental conclusion to be drawn is that pituitrin is not an antagonist of insulin.

4. The theory has been advanced that pituitrin, by virtue of its vasoconstrictor action, retards the absorption of insulin given subcutaneously and, in this manner, prevents insulin from acting on the blood sugar. Experiments are reported which show that pituitrin does not influence the absorption of phenolsulphonphthalein injected subcutaneously. This theory is, therefore, untenable. The mechanism by which pituitrin counteracts the action of insulin, given subcutaneously, on blood sugar appears unexplained.

5. The action of pituitrin in partially neutralizing the action of insulin administered subcutaneously is of physiologic interest only. It need not be taken into consideration in determining insulin dosage in diabetic patients who are receiving pituitrin simultaneously.

6. Epinephrine markedly antagonizes the action of insulin, administered intravenously or subcutaneously, on the blood sugar of diabetic patients receiving dextrose. In the doses used, the neutralization of the action of insulin was complete.

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THE EFFECTS OF ACETYL-BETA-METHYLCHOLINE IN HUMAN SUBJECTS WITH LOCALIZED LESIONS OF THE CENTRAL NERVOUS SYSTEM

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IN a recent paper by Stavraký²⁶ it was shown on experimental animals that aseptic removal of various portions of the cerebral hemispheres resulted in a prolonged sensitization of the remaining parts of the nervous system to intravenous injections of acetylcholine. This sensitization to chemical stimulating agents occurred in neurones which were directly connected with the removed portions of the brain and manifested itself in various specific patterns of response. Particularly striking results were obtained in cats in which the frontal lobes were removed (the motor cortex being included in the removal). Injections of acetylcholine in these animals resulted in characteristic motor manifestations and signs of excitation of the sympathetic nervous system, such as dilatation of the pupils, protrusion of the claws and erection of hair, all these phenomena occurring contralaterally to the removal.

In an extension of these experiments it was decided to study the effects of a suitable choline ester in human subjects with corresponding lesions of the central nervous system. Acetyl-beta-methylcholine was chosen in preference to acetylcholine because of its wide clinical use, extreme potency, and minimum nicotine-like action on the sympathetic ganglia. (Hunt and Taveau,¹⁷ Hunt,¹⁵ Villaret, Justin-Besançon, Cachera and Said,²⁷ Simonart,²³ Comroe and Starr,⁶ Starr, Elsom and Reisinger,²⁴ Abbott,¹ Hunt and Renshaw,¹⁶ Weiss and Ellis,³⁰ Myerson, Loman and Dameshek,²¹ Dameshek, Loman and Myerson,⁹ Altman, Pratt and Cotton² and others).

During the progress of the work it was found that best results were obtained with intramuscular injections of acetyl-beta-methylcholine instead of the subcutaneous ones employed in the majority of the previous investigations. The intramuscular injections gave quicker and sharper responses, the erythema and sweating often spreading down to the finger tips and toes of the tested subjects. As side effects of such injections, 3 of 19 persons became somewhat asthmatic, 1 complained of a feeling of tightness and pain in the chest, and 1 felt nauseated and experienced some pain in the epigastrium; all these symptoms were quickly relieved by a subcutaneous injection of 1/100 gr. of atropine sulphate.

The neurologic findings obtained with this method of study are in general agreement with the results reported in experimental animals and will be the subject of the present communication.

Methods. The effects of acetyl-beta-methylcholine chloride (Mecholyl Merck) were studied in 12 male patients with lesions of the rostral portions of the cerebral hemispheres or with signs of involvement of the upper motor neurones. The various lesions were: 2 brain tumors; 1 frontal lobectomy for a tumor; 7 head injuries in which damage was localized to the frontal lobe with or without extension of the injury to the motor cortex; 1 case of a lesion following an attack of cerebrospinal meningitis with residual signs of unilateral involvement of the pyramidal system; and 1 case of injury to the spinal cord. As controls, 6 normal persons and a patient with Raynaud's disease were studied in a similar manner.

Injections of 8 to 25 mg. of mecholyl dissolved in 0.3 to 1.0 cc. of distilled water were given into the deltoid muscle and were repeated in each patient at least on two or three occasions. The tested subjects were males of excellent physique, as they were associated with the armed forces of Canada. They were stripped and placed in a recumbent position on a table or a bed facing the window in order to obtain a dispersed and uniform lighting of the two pupils. The minimal amount of light in the ophthalmoscope necessary to produce a contraction of the pupils by flashing the light separately into each eye was then determined, and a complete neurologic examination was carried out before and during the action of mecholyl.

Results. *Effect of Mecholyl in Normal Males.* The sensitivity of different individuals varied considerably. As a rule, within 20 to 30 seconds after the injection of 8 to 10 mg. of mecholyl, the tested subject experienced a sensation of heat in the face. This was followed by a flushing of the face and neck, the erythema spreading rapidly to the chest and back and then to the extremities. It frequently extended to the fingers and toes but decreased in intensity towards the lower part of the body. An impression was gained that exposure to cold and possibly smoking or excitement had a tendency to cause an incomplete spreading of erythema over the apices of the extremities. The flushing reached its maximum about 2 minutes after the injection and was accompanied by widespread diaphoresis and often by rhinorrhea, salivation and lachrimation. Later in the response, shivering usually occurred and a slight increase of tendon jerks was occasionally noted. In 2 very sensitive individuals the first signs of flushing were accompanied by a slight transient dilatation of the pupils. Most of the features of the reaction described were terminated within 5 to 10

minutes after the injection, but larger quantities of mecholyl gave more pronounced reactions.

Effect of Mecholyl in Patients with Lesions of the Rostral Portions of the Cerebral Hemispheres. In 11 patients with lesions of the frontal lobe with or without involvement of the motor cortex, the injection of mecholyl produced an asymmetrical response. In 9 patients the erythema spread more rapidly on the side of the lesion and stopped in the upper extremity at the wrist or at the metacarpo-phalangeal joints, the hand or the fingers becoming very pale. In the lower extremity the flush extended to the ankle or to the dorsum of the foot. Contralaterally the spreading of the flush was delayed and the erythema stopped high on the limbs. Frequently the arm from the elbow down and the entire leg became pale, this pallor of the contralateral extremities developing more slowly than the ipsilateral flush. It became pronounced 2 minutes after the injection and reached its acme about $1\frac{1}{2}$ minutes later, gradually replacing the initial erythema. In 3 patients the pallor spread almost over the whole side of the body opposite to the lesion, only the chest above the nipple line and the face remaining flushed on that side. About $3\frac{1}{2}$ to 4 minutes after the injection, the contralateral blanching was often followed by a delayed flush, this occurring after the general erythema had largely subsided (see Fig. 1).

During the reaction the contralateral extremities were markedly colder than the ipsilateral ones. Also there was an asymmetrical distribution of sweating which was less pronounced on the side of the body opposite to the lesion. In the early stages of the response a delay in the sensation of heat on the opposite side of the face and a transient dilatation of the contralateral pupil were noted in 7 patients. In 4 of them both pupils dilated slightly but the contralateral effect was more marked. On 3 occasions the contralateral pupil became irregular in outline and did not constrict as readily to light as the ipsilateral one.

In cases in which the lesions extended to the motor or premotor cortex, muscular tremors, slight involuntary movements, an increase in spasticity, pronounced hyperreflexia, clonus of the wrist, ankle, and patella, and prominence of pathologic reflexes on the opposite side of the body characterized the later stages of the reaction.

The blanching of the extremities was most noticeable after the injection of 8 to 10 mg. of mecholyl, but the other features were more marked when larger quantities were administered. All the phenomena described were most pronounced in the case of lesions which involved the motor and premotor areas but a considerable asymmetry of the response was observed in frontally situated injuries in which no objective neurologic signs were present.

Three case reports of patients with different types of lesions will serve as an illustration. The first 2 cases demonstrate the reaction to mecholyl in a traumatic lesion of the motor cortex, and in a tumor involving the motor area of the brain. The 3rd case shows the effect of mecholyl after an injury to the premotor cortex.

CASE 1. Gnr. R.J., aged 21, on April 1, 1942 sustained a gunshot wound to the right side of the head. He was operated upon in England and on recovery was transferred to Westminster Hospital. When first seen on November 16, 1942, the patient had a typical hemiplegic gait and a scar which extended from a point anterior to the right ear to within 2 cm. of the midline. A depressed, pulsating bony defect $6 \times 7\frac{1}{2}$ cm. in area was noted under the scar.

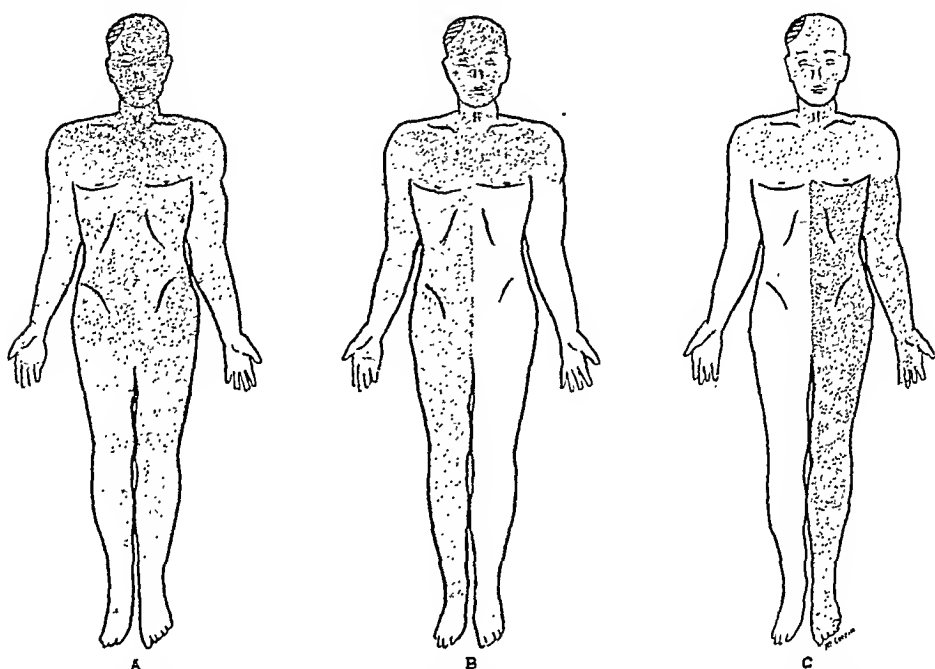


FIG. 1.—Distribution of erythema on intramuscular injection of 8 to 10 mg. of mecholyl in a patient with a left-sided hemiplegia resulting from a gunshot wound of the head. The bullet traveled from below up, destroying almost exclusively the motor area of the right cerebral hemisphere (Case 1). A, Distribution of erythema 1 to 2 minutes after the injection. B, Distribution of erythema $3\frac{1}{2}$ minutes after the injection. Note the spreading pallor over the left side of the body. C, Initial erythema recedes 4 to $4\frac{1}{2}$ minutes after the injection and a secondary flush appears over the previously pale regions on the left side.

On examination, a complete left hemiplegia was present involving the lower face, arm, and leg. Spasticity, increased tendon jerks, wrist and ankle clonus, plantar extension and a positive Hoffman sign, diminution of the corneal and abdominal reflexes, and a disturbance of cortical sensations were present at that time on the left side of the body. The paralyzed extremities felt clammy and cold and the left pupil was slightly larger than the right one, though both reacted to light. On November 5, 1943 when the patient was last examined, considerable recovery of sensation was noted in the paralyzed limbs, the corneal and abdominal reflexes were present and equal, the spasticity had decreased, the limbs being flaccid at the elbow and knee but a moderate spasticity of the hand and foot persisting. The pupils were of equal size, although the left one still had a tendency to dilate more briskly than the right one. In spite of the improvement the response to mecholyl was at this time even more asymmetrical than on the two previous occasions.

Effect of Mecholyl. (November 5, 1943). An intramuscular injection of 8 mg. of mecholyl was followed in 20 to 25 seconds by a sensation of heat in the right side of the face and by a slight but definite dilatation of the left pupil. Immediately following, the face, chest and extremities flushed rapidly and 2 minutes after the injection the erythema spread to the metacarpo-phalangeal

joints and to the dorsum of the foot on the right side. On the left side it extended to halfway between the wrist and the elbow, and to approximately 5 inches above the ankle, the left hand and foot becoming very pale and a sharp line of demarcation developing between the pallor and the flush. The pallor gradually ascended and 3½ minutes after the injection it had risen to 7 inches above the elbow on the left arm and involved the whole left leg and left lower portion of the body. The pale parts remained cold and dry, whereas the flushed regions were warm and covered with beads of perspiration. In half a minute the initial erythema largely subsided, whereas the pale hemiplegic parts of the body suddenly flushed. This delayed flush of the paralyzed side lasted less than 1 minute. At this time the spasticity of the paralyzed limbs was much greater than before the injection of mechohyl and there were tremors and some slight movements in the left arm. On another occasion an injection of 16 mg. of mechohyl resulted in much more pronounced tremors and athetoid-like movements in the paralyzed limbs and in an involuntary attempt to raise the stiffened semiflexed arm.

CASE 2. L/Cpl. S.C., aged 49, on June 14, 1943 was admitted to the Westminster Hospital with a 2 weeks history of epileptiform attacks. The seizures were of a Jacksonian type, recurred at the rate of 2 or 3 a week and were largely localized to the left leg. The attacks were not accompanied by a loss of consciousness but they were associated with a "sickening feeling" in the epigastrium, and numbness and tingling in the left hand followed by weakness of the extremities on that side of the body. On examination a bronchogenic carcinoma was found in the left lung and the neurologic condition diagnosed as due to a metastatic tumor in the brain. The patient died on September 2, 1943 from pulmonary complications. The diagnosis was verified at autopsy, the primary carcinoma being situated in the upper lobe of the left lung and a metastasis of 4 x 6 cm. in cross-section was found in the precentral gyrus of the right cerebral hemisphere.

On July 2, 1943 preceding the injection of mechohyl, the patient was clear mentally, well oriented, and coöperative. Cranial nerves were negative except for a moderate sclerosis of the retinal blood-vessels Arcus senilis; tendon jerks were increased on the left side of the body with a suggestion of ankle clonus and positive Babinski and Oppenheim signs in the left foot; and the cremasteric and abdominal reflexes were diminished and easily fatigued on the left. All movements of the extremities were possible, but there was a definite weakness of the left hand and leg and the movements were awkward. There was also a slight wasting of the muscles of the left leg (right thigh 20¼", left 20¼"; right calf 13½", left 13¼"). The tone of the muscles of the left arm and leg was diminished and during walking the patient slightly dragged that leg while the arm hung limp, the associated movements being absent in it. There was no apparent sensory disturbance outside of some impairment of stereognosis and two point sensibility on the left.

Effect of Mecholyhl (July 2, 1943). Twenty-five to 30 seconds after the injection of 10 mg. of mechohyl the patient experienced a sensation of heat in the face and neck which was followed by flushing of the face, the flush then spreading over the body. Three minutes after the injection the bright color extended symmetrically over both arms and the upper parts of the body, stopping on the hands at the metacarpo-phalangeal joints. On the right leg it descended to about 3 inches above the ankle, but stopped sharply at the left groin, the left leg remaining pale. Three and a half minutes after the injection, the lower left side of the body blanched rapidly and a sharp line of demarcation developed between the left and the right side of the chest and of the abdomen, the pallor stopping under the left nipple. The pale left side of the trunk and the left leg were cold and there was no sweating over these parts, whereas the flushed right half of the body was warm and densely covered with beads of perspiration. In half a minute the flush over the right side and over the upper left part of the body began to fade. The pallor over the lower part of the left side also wore off and was replaced by a delayed flush which lasted about a minute. A study of the reflexes at this time showed a greater asym-

metry of response on the two sides of the body than before the injection and a sustained ankle clonus on the left. The patient became asthmatic and 1/100 gr. of atropine sulphate was injected which quickly relieved the condition. After the administration of atropine the ankle clonus disappeared and could not be elicited on repeated examinations, but the plantar response remained extension on the left. No pupillary response of any kind was observed in this patient.

CASE 3. LAC W.B., aged 20, on October 9, 1942 was hit on the head by an aeroplane propeller and was admitted to the Westminster Hospital on October 10, 1942 in an unconscious condition with a lacerated wound of the scalp 19 cm. long extending from 2 cm. posterior to the right orbit up to and over the mid-line of the vault of the head. The wound was explored, and loose fragments of bone, blood clots and oozing brain tissue removed, sulfanilamide powdered into the wound and the latter closed with interrupted sutures. The patient regained consciousness 48 hours after admission but had no control over the rectum and bladder for 22 days after the accident. For the next 2 months there was marked emotional instability and he exhibited a difference in the skin temperature on the two sides of the body, the left arm and leg feeling clammy and cold and the temperature in them being as much as 2° F. lower than in the extremities of the right side. For the same length of time the plantar response was extension on the left and flexion on the right side, this in the absence of any other abnormal neurologic findings except for a suggestion of a Horner's syndrome on the left.

Effect of Mecholyl (November 27, 1942). Twenty-five to 30 seconds after the injection of 8 mg. of mecholyl the patient experienced a sensation of heat on the right side of the face and there was a slight dilatation of the pupils, predominantly of the left one. This was followed by a flushing of the skin which in 2 minutes spread on the right side to the metacarpo-phalangeal joints and to approximately 5 inches above the ankle, whereas on the left side it extended to 3 inches proximal to the wrist and to the middle of the thigh, the lower parts of the extremities being very pale. About 3½ minutes after the injection the flush over the right side of the body receded while the lower left side of the body and left leg suddenly became pale and then flushed for a period of about half a minute. Simultaneously there was a slight change in the size of the pupils, the left one contracting and the right one seemingly increasing in size; then the right leg became flushed once more. Bilateral plantar extension, bilateral ankle clonus and patellar clonus on the right were elicited at this stage of the reaction (prior to the injection of mecholyl the Babinski sign was positive only on the left and no clonus was elicited at all). The injection was repeated on November 30, 1942 with similar results.

On December 18, 1942 preceding the patient's discharge from the hospital the temperature over the two halves of the body was practically equal and the neurologic examination negative, only a slight Horner's syndrome persisting on the left. On injection of 10 mg. of mecholyl the distribution of the erythema was almost symmetrical with some blanching of the hands and feet, but towards the end of the reaction there was an intermittent blanching and flushing of the two legs and a reappearance of bilateral ankle clonus, patellar clonus on the right and an indefinite plantar response on the left.

It is interesting to note that in the last case, upon the injection of mecholyl, the response was to a large extent bilateral. This bilateral distribution of various signs was even more striking in another case of extensive injury to both frontal lobes and must be regarded as an indication of a contre-coup damage of the opposite side of the brain. More difficult to understand was a case of an infiltrating brain tumor in which, as verified at autopsy, a medulloblastoma growing from the anterior part of the corpus callosum extended into the parietal and temporal regions of the right cerebral hemisphere and into the floor

of the left lateral ventricle. In this patient with a left sided hemiplegia, the injection of mecholyl caused a dilatation of the right pupil and a blanching predominantly of the right extremities.

Effect of Mecholyl in a Case of Spinal Injury. Mecholyl was injected into a patient recovering from a quadruplegia which followed a fracture dislocation of the cervical spine sustained in the collision of a staff car with a heavy gun during a blackout in England. The effect of mecholyl was so interesting that a brief case report and a description of the injection will be given.

CASE 4. Cpl. B.J., aged 42, on March 15, 1942, sustained an injury of the spinal cord at the level of the cervical 6 to thoracic 1 segments, resulting in an almost complete paralysis of a quadruplegic type. This was accompanied by a corresponding level of anesthesia and loss of bladder control. The diagnosis of a fracture dislocation of the 4th cervical vertebra was made. It was reduced surgically and the patient showed gradual improvement, regaining bladder control and partial function of his extremities. When seen on January 11, 1943 he could walk across the room without aid, but on examination showed considerable impairment of movements with bilateral spasticity, hyper-reflexia, bilateral positive Hoffman and Babinski signs, and persistent sensory changes. All these findings were more pronounced in the upper extremities; in particular the recognition of passive movements in the fingers was grossly impaired but was good in the toes. The patient's chief complaint was that of a severe burning pain in the hands, which on examination looked very red, felt hot and perspired profusely.

Effect of Mecholyl. An injection of 16 mg. of mecholyl produced a symmetrical flushing which was more pronounced in the upper part of the body. However, in the upper extremities the erythema stopped 3 inches below the elbows, the color of the hands and lower forearms changing from bright red to pale purple. In addition, the hands became cool to the touch and dry, the perspiration on the palms and fingers stopping abruptly. The burning sensation of which the patient had complained so bitterly before the injection completely disappeared, all the signs returning $1\frac{1}{2}$ hours later. Subsequently this patient was injected with various quantities of mecholyl (8 to 25 mg.) on numerous occasions, invariably obtaining some relief from the burning pain in his hands.

Effect of Mecholyl in an Angio-spastic Derangement. A somewhat similar response to mecholyl as the one noted in cerebral lesions was found to occur in a typical case of Raynaud's disease. In this patient mecholyl was injected during an angio-spastic attack which involved the index and middle fingers of the left hand. Preceding the injection the two fingers felt numb, were cold and had a wax-like appearance on the dorsal surfaces and blue-black patches on the palmar aspect. By the 2nd minute following the injection of 10 mg. of mecholyl the erythema spread over both hands, excluding the left index, middle and ring fingers and the right index finger, which all became very pale. On the right leg the flush descended to the ankle, but the left leg remained pale from the groin down. The erythema began to subside $3\frac{1}{2}$ minutes after the injection, and when the right leg and the lower part of the body regained their normal color the left leg rapidly became flushed. Four to 5 minutes after the injection the pallor in the fingers gradually began to diminish and 2 or 3 minutes later the vascular spasm in the affected fingers of the left hand completely wore off and both hands acquired a normal appearance.

Discussion. The phenomenon of sensitization of denervated tissues to chemical stimulation is well known. In regard to the central nervous system Claude Bernard³ drew attention to the fact that strychnine can cause movements in paraplegic limbs while Cannon,⁴ Cannon and Haimovici,⁵ and Stavraky²⁶ established experimentally that a selective sensitization to acetylcholine takes place in partially denervated neurones of the brain and spinal cord. The results obtained during the present investigation can be interpreted in the light of these findings.

In normal individuals mecholyl is predominantly parasympathicomimetic and probably its effects are largely of a peripheral nature. However, in cases of damage to the motor and premotor cortex as well as to the highest levels of the sympathetic nervous system (Fulton¹¹), a sensitization to chemical agents takes place in the next links of the chains of descending neurones, and the sensitized neurones are stimulated by mecholyl to such an extent that their excitation overshadows the usual peripheral effects of this substance in certain parts of the body. If the sequence of vasomotor changes which occurs in patients with lesions of the frontal lobe following an injection of mecholyl is considered from this point of view, it may be suggested that first an erythema of a peripheral nature develops, then localized vasoconstriction sets in due to stimulation of sensitized sympathetic centers by mecholyl (the vasoconstriction occurring mostly contralateral to the lesion), and finally, when this latter subsides, a secondary flush appears in regions in which vasoconstriction interferes with the circulation, thus possibly leading to retention of mecholyl. The movements which occur in the paralyzed limbs, an increase of spasticity and an exaggeration of reflexes as well as other manifestations may be due to a sensitization of motor neurones.*

With the exception of the pupillary reaction, which varies, the effects of central stimulation develop slowly, and become prominent 2 to 4 minutes after an injection of mecholyl, the response in this way resembling that following intravenous injections of acetylcholine in the cat (Stavraky²⁶). Protracted effects of injections of acetylcholine on the central nervous system have been noted also in intact animals. Keith and Stavraky¹⁹ have shown in certain forms of experiments that acetylcholine prevents the onset of convulsions induced by thujone. Coombs and Cope⁷ have confirmed this observation in regard to camphor and have emphasized the fact that the effect of acetylcholine on the central nervous system, after intravenous injections of the latter, persisted as long as 10 minutes, while Ellis and Weiss,¹⁰ Lanari²⁰ and Harvey, Lilienthal and Talbot¹⁴ observed that erythema and diaphoresis in an extremity lasted for 10 to 15 minutes after intra-

* Significantly, Cooper⁸ in an attempt to treat upper motor neurone lesions with intraoral administrations of acetyl-beta-methylcholine, noted that an increase of spasticity took place in the paralyzed limbs. (A review of the literature on the question of treatment of neurologic conditions with choline derivatives can be found in a recent article by Ward, A. A., and Kennard, M. A., *Yale J. Biol. and Med.*, 15, 189, 1942.)

arterial injections of acetylcholine in human subjects. This slow type of response is particularly interesting in the case of the action of acetylcholine in view of its rapid rate of destruction in the body.

The blanching of the hands and discontinuance of sweating, as well as the relief from burning pain, which took place after the injection of mecholyl in the case of spinal injury (Case 4) were outstanding examples of the prolonged effect of mecholyl on sensitized nerve cells located in the isolated spinal sympathetic centers or peripheral sympathetic ganglia, the vasoconstriction caused by the stimulation of these structures probably accounting for the relief from pain and cessation of sweating, though as regards the latter, conditions may be more complex (Kahn and Rothman).¹⁸

The reaction in the case of Raynaud's disease had certain similarities with that observed in patients with lesions of the central nervous system. It is interesting that Starr²⁵ noted a different response to mecholyl given by injection or by the oral route in some peripheral vascular derangements, the former diminishing the circulation in the affected limbs while oral administration of mecholyl increased it. Page,²² who suggested a central action of mecholyl, noted that upon subcutaneous injection it failed to cause vasodilatation in the hands and feet of hypertensive patients, whereas Goldsmith¹² observed a marked vasodilatation in the digits upon oral administration of mecholyl to a similar group of patients. Finally, Villaret and Even²⁸ and Villaret and Justin-Besançon²⁹ described a spectacular diminution of night sweats in tuberculous patients following injections of acetylcholine. This effect is most interesting inasmuch as in normal individuals acetylcholine causes an increased diaphoresis (Ellis and Weiss,¹⁰ Harvey, Lilienthal and Talbot¹⁴ and others). It appears possible that all these observations point to an increased irritability of certain groups of nerve cells to chemical agents in a variety of pathologic conditions as well as in the case of structural lesions of the central nervous system.

If this view is adopted, also the difference in the response to acetylcholine of epileptic patients and normal human subjects becomes readily understood. Williams³¹ described a marked increase in the electro-encephalographic manifestations of epilepsy after injections of 0.25 mg. of carbaminoylcholine or 30 to 60 mg. of acetylcholine and presented a record of a clinical epileptic attack induced by means of an intravenous injection of 30 mg. of acetylcholine. No similar results could be obtained in normal controls, and in order to produce in non-epileptic human subjects (mental patients) tonic extensor spasm analogous to those described in intact cats (Stavraky²⁶), Harris and Pacella¹³ found it necessary to inject quantities of acetylcholine ranging from 220 to 500 mg.

Summary and Conclusions. In patients with lesions of the frontal lobe, intramuscular injections of acetyl-beta-methylcholine (Mecholyl) resulted in contralateral signs of excitation of the sympathetic nervous system, such as a slight dilatation of the pupil, and blanching, coldness

and diminution of sweating over the extremities and lower part of the trunk.

In cases in which the premotor and motor areas were involved, signs of excitation of the sympathetic nervous system were particularly prominent. In addition there were some motor manifestations, an increase of spasticity and the exaggeration of reflexes. All these occurred on the side of the body opposite to the lesion.

These effects of mecholyl are interpreted as resulting from a selective sensitization to chemical stimulating agents of partially isolated nerve cells situated in the chains of descending neurones of the brain and spinal cord.

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SPONTANEOUS SPLENIC RUPTURE IN INFECTIOUS MONONUCLEOSIS

A CASE AND PATHOLOGIC REPORT

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INFECTIOUS mononucleosis is usually a self-limited benign disease, but it may be complicated, as in the following case, by spontaneous rupture of the spleen.

Case Report. The patient, a 33 year old white male, American born, of English descent, occupation bank clerk, had been in good health and detailed questioning failed to reveal any history of splenic disorder. On May 19, 1943, he developed a mild sore throat and found that he was running a low grade fever. The sore throat subsided after 2 days but the fever persisted and gradually increased. He was first seen on May 30; chills, sweats and marked weakness constituting the chief complaints. The temperature was 100° F.; there was slight but definite tenderness in the upper right abdominal quadrant, otherwise the physical examination revealed nothing remarkable. By the next day, upper right abdominal pain was a conspicuous complaint, the liver edge was found to be 3 fingers' breadth below the right costal margin, and slight jaundice was noted. There was no lymphadenopathy.

The patient was hospitalized for observation. The admission blood count was as follows: hemoglobin 98% (Dare), red count 4,900,000, and the white count 7800 (75% neutrophils and 25% lymphocytes). The urine examination presented nothing abnormal except the presence of bile. The sedimentation rate was 19 mm. in the first hour. Agglutination tests for typhoid, paratyphoid, brucella and proteus OX-19 were negative.

On June 2 the white count was found to be 17,900 (40% each of neutrophils and lymphocytes and 20% large mononuclear cells). By this time jaundice was marked and the liver edge was 5 fingers' breadth below the costal margin. Exquisite tenderness was present in both upper abdominal quadrants. The inguinal and axillary lymph nodes had become enlarged and tender. The fever ranged from 100° to 101° F. Morphine was necessary for the control of abdominal pain. By June 3 the white count had risen to 34,300 (25% neutrophils, 58% lymphocytes—80% of which were large—and 17% large mononuclears). The heterophil antibody test (Paul and Bunnell) was positive at a dilution of 1:3584. Cervical lymphadenopathy was noted for the first time and the spleen was palpable 4 fingers' breadth below the left costal margin. Tenderness in the upper abdomen continued to be most marked.

Between the dates of June 3 and 5, the patient seemed to be improving as the jaundice, abdominal tenderness and fever were receding. At 6.30 A.M., however, on June 5, he was awakened from sleep by a stabbing, agonizing pain in the mid-epigastrium and back. He promptly went into shock. The

abdomen was rigid and tender. His condition steadily improved as 500 cc. of blood plasma and 1000 cc. of 5% glucose in normal saline were given intravenously. Because of the abdominal findings and symptoms, laparotomy was done 14 hours after the onset of the attack. The abdominal cavity was filled with blood which welled out of the incision, making inspection of the viscera impossible. By palpation a large tear near the hilus of the spleen was discovered, and the spleen was removed. Blood plasma was given throughout the operative period as fast as it could be made to flow (500 cc. in all). Surgery was followed immediately with another 250 cc. of plasma and then by 500 cc. of whole blood. Early the next morning another transfusion of 500 cc. of whole blood was given.* The condition of the patient throughout the operative and immediate postoperative period was surprisingly good. Twelve hours after the operation, the hemoglobin was 47%; red blood cell count 3,150,000, leukocyte count 30,800 (45% neutrophils, 54% lymphocytes, 1% eosinophils). Convalescence was satisfactory and the patient was discharged from the hospital on June 17. A blood count 1 month later was: hemoglobin 84%, red cell count 3,820,000 and white cell count 11,100 (45% neutrophils, 43% lymphocytes, 6% large mononuclear cells, 6% eosinophils). At this time the patient was up and about at will and he was discharged.



FIG. 1.—Convex surface of the spleen, showing torn capsule with protruding pulp.

Pathologic Report. The spleen weighed 460 gm., measuring 14.5 by 10 by 6 cm. The capsule was thin, smooth and tense. A ragged tear along the anterior margin, 4 cm. in length with protruding soft red pulp, was noted. This opening through the capsule extended obliquely across the convex surface for 2 cm. and measured 2.5 cm. in depth. Its margins were hemorrhagic in part, and surfaces made by cutting showed several solid masses of red blood clot embedded in the splenic substance of the region. These clots tended to be pyramidal in outline and measured from 0.5 to 2 cm. in their greatest dimension (Fig. 1).

* Blood plasma and whole blood were both obtained from the Belle Bonfils Memorial Blood Bank.

Surfaces exposed by cutting through the spleen at points removed from the rupture revealed a homogeneous dull red pulp, which tended to bulge and was soft and friable. Malpighian corpuscles were not grossly evident.

Microscopic Examination (Zenker's fluid and formalin fixation; stained with hematoxylin and eosin, phloxine-methylene blue, pyronin methyl green, and Giemsa; Bielschowsky, Foot's modification, for reticulum): Giemsa-stained impression smears from the unfixed spleen contained many small and large lymphocytes, and fewer neutrophilic and eosinophilic granulocytes.

The capsule and trabeculae of the spleen appeared normal except where they had been distorted by hemorrhage into the adjoining substance. The reticulum appeared normal except where it was disrupted or hemorrhagic. The arterial branches and corpuscular arterioles appeared normal. The Malpighian corpuscles were small and lacked germinal centers.

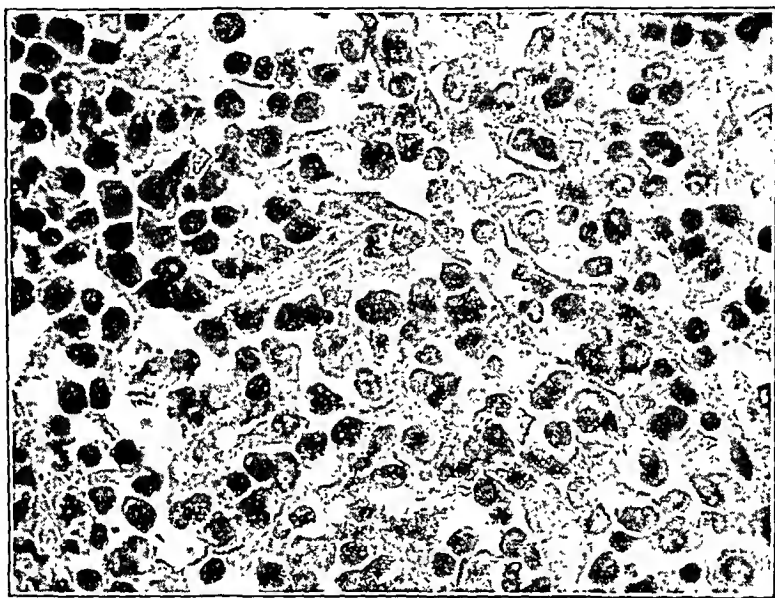


FIG. 2.—Section of red pulp showing large lymphoid cells with spheroidal nuclei, phloxine methylene blue stain ($\times 250$).

The sinusoids were moderately full of blood containing many leukocytes, including neutrophils, occasional eosinophils and lymphoid cells. The distribution of cells between sinusoids and pulp spaces was nearly equal, and tended to obscure the sinusoidal boundaries. In general, the red pulp contained numerous small lymphocytes together with larger lymphoid cells having compact, spheroidal, deep staining nuclei and abundant non-granular cytoplasm (Fig. 2). Macrophages with indented, fusiform, or oval reticular nuclei and prominent nucleoli were also numerous. Phagocytosis of nuclear debris was evident in these cells. Plasma cells were present, and tended to occur in small clusters. A few large multinuclear cells resembling megakaryocytes were seen. Eosinophils were fairly numerous in the pulp spaces, while neutrophils were less common here than in the sinusoids. The endothelial cells lining the sinusoids were large, with faintly eosinophilic cytoplasm.

No definite evidence as to the direct cause of the fracture or hemorrhage in this spleen was obtained from the pathologic examination. It is possible that a local lesion previously existed at the site of the initial hemorrhage; but if so, it had been obliterated.

While the clinical course prior to the appearance of diagnostic signs and laboratory findings may have been obscure and unusually long,

the chief interest in this case centers around the spontaneous rupture of and the pathologic findings in the spleen of a patient with infectious mononucleosis. To our knowledge, the literature contains but 1 report of such a complication. In 1941, King¹ reported the case of a young man with infectious mononucleosis, who at the height of his disease suddenly developed the picture of an acute abdominal complication with shock. Splenectomy was performed and the patient recovered. The paper includes a pathologic study of the spleen by Dr. Shields Warren.

It seems probable that the spleen shares in the cellular change taking place in the lymphoid tissues during the course of infectious mononucleosis. These changes have been described by Gall and Stout² as consisting of 3 preëminent features: (1) marked proliferative activity in the pulp, which serves to obscure the margins of the follicles; (2) extensive but distinctly focal proliferative activity of clasmato-cytes; (3) appearance throughout the pulp, on the edges of the germinal centers and in the sinuses, of large numbers of the specific "infectious mononucleosis cells." The use of Zenker-fixed nodes, stained with phloxine-methylene blue, aids in recognition of these cells, in the opinion of these authors.

Comparative studies of the spleen using a variety of stains, including phloxine-methylene blue, shows a general similarity to the changes described in lymph nodes. The follicular hyperplasia, which they describe as transient, was lacking in the spleen. The red pulp was crowded with lymphoid cells of all types, tending to obscure the sinusoidal structures, but evidence of proliferation of these cells *in situ* was not seen. Proliferative activity of clasmatocytes on a large scale was not demonstrable.

Large lymphoid cells corresponding to those described as "infectious mononucleosis cells" are fairly numerous in both the sinusoids and the pulp spaces, and are rather distinctively stained by phloxine-methylene blue.

A search for alterations in the stroma and vascular apparatus of this spleen revealed nothing of significance.

Conclusion. Spontaneous rupture of the spleen should be thought of when signs of a very acute intra-abdominal complication suddenly appear during the acute phase of infectious mononucleosis.

Pathologic examination of the spleen removed at operation disclosed rupture and hemorrhage with an increase in the lymphoid elements, and the presence of an atypical cell similar to that of infectious mononucleosis as found in the peripheral blood.

Since this report was submitted, another instance of spontaneous rupture of the spleen in infectious mononucleosis, with autopsy findings and histologic studies has been reported by E. E. Zeigler, *Arch. Path.*, 37, 196, 1944.

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PROGRESS OF MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY

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THE RELATION OF STREPTOCOCCI TO HUMAN DISEASE: IMPORTANCE OF IDENTIFICATION AND NOMENCLATURE

I. THE BETA HEMOLYTIC STREPTOCOCCI OF GROUP A

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AND

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THIS review is a plea for the recognition of bacterial species only in so far as the application of proper names yield clarity of thought and expression. No one knows what a bacterial species is. Among the higher plants and animals one has the aid of diverse morphology and the non-fertility of members of different species with each other. But among the bacteria the one is meagre and the other lacking. In his classical work on Immunity and Blood Relationship, Nuttall¹⁸ (1904) showed that serologic results in large measure confirm zoölogic classification. Systematic bacteriologists find serology one of their most valuable tools. Nevertheless, they are still largely dependent upon physiologic activity, including pathogenicity, to differentiate one bacterium from another. If the minute structure of an enzyme or protein molecule could be seen, doubtless it would be found that diverse physiologic function is determined by morphologic difference. Biology is chemistry; chemistry is physics; and physics is the relation of objects in space, if there is any space. Every biologist assumes that species are relatively stable; they are the result of evolution which he has no reason to believe has been suspended, but which proceeds so slowly or so intermittently that it need not deter the giving of useful names to the species which he observes. Names are labels used for convenience in description and, if possible, to indicate genetic relationship.

Typhoid fever, diphtheria, tetanus, tuberculosis, plague, gonorrhea, anthrax, Asiatic cholera; these are specific diseases, each caused by a single species of bacteria. Because of this specificity, the identification of the microörganism with the disease and the ability to reproduce the disease experimentally serve to identify the bacterium although morphologic, cultural and serologic studies serve to make the description more

nearly complete and are valuable aids in bacteriologic diagnosis. Peritonitis, pneumonia, puerperal sepsis, sore throat, otitis media, arthritis, endocarditis, meningitis, osteomyelitis; these are not specific diseases and each may be caused by a number of different species of bacteria. The naming of a species of bacteria for a non-specific disease does not constitute an adequate description without morphologic, cultural and serologic studies.

Most of the streptococcal infections fall into the category of non-specific diseases. Furthermore, most of the pathogenic streptococci are "opportunistic" pathogens, frequently harbored by normal individuals and producing disease only when opportunity is offered by accident, lowered resistance, or increased virulence of the microorganism brought about by passage through susceptible individuals. Of the human streptococcal diseases, the 2 which have the best claims for specificity are erysipelas and scarlet fever and yet, as will be seen, it appears that more than 1 species of streptococcus may cause each of these.

Streptococcus, as the name of a genus, was first used by Rosenbach²⁰ (1884) (Buchanan,⁶ 1925) although previously many authors (Billroth, Cohn, Winge, Klebs, Rindfleisch, Von Recklinghausen, Crookshank, Orth, Pasteur, Koch, Ogston, Fehleisen) had observed cocci in chains and had used the name streptococcus or its equivalent as a morphologic term. In 1884 Rosenbach,²⁰ in a study of microorganisms from wound infections, employed the name *Streptococcus pyogenes*. Although Rosenbach's description was not adequate to distinguish this streptococcus from other species as we now know them, the source of his strains makes it highly probable that most of them were *Streptococcus pyogenes* as it is known today. Marmorek¹⁷ (1902) noted that most of his strains of streptococci of human origin laked rabbit blood added to "peptone bouillon" and formed zones of hemolysis about colonies in blood agar. Andrewes and Horder¹ (1906) correlated the fermentation of sucrose, lactose and salicin, and failure to ferment mannitol with production of hemolysis. Lancefield¹⁶ (1933) placed those of her strains of hemolytic streptococci which obviously were *Streptococcus pyogenes* in her serologic Group A. These may be regarded as the essential emendations to the description of *Streptococcus pyogenes* Rosenbach²⁰ 1884, *cm.* Marmorek¹⁷ 1902, Andrewes and Horder¹ 1906, Lancefield¹⁶ 1933; a beta hemolytic streptococcus which ferments sucrose, lactose and salicin, does not ferment mannitol, and belongs to serologic Group A, although many other authors have added correlative and useful tests (Brown⁴ 1919, Ayers and Rupp² 1922, Edwards⁷ 1933, Tillett and Garner²³ 1933, Evans 1936⁸).

Streptococcus pyogenes, as defined above, is the species most frequently found in acute human streptococcal infections; including wounds, erysipelas, scarlet fever, septic sore throat, cellulitis, puerperal sepsis, septicemia, and sometimes in peritonitis, meningitis, endocarditis and many localized lesions. Less frequently one finds other beta hemolytic streptococci in many of these pathologic conditions.

It would be to the advantage of scientific medicine and bacteriology to have these differences recognized and reported rather than concealed under a single name. Too often simplification of nomenclature is attained by ignoring differences. Rolly¹⁹ (1911-1912) introduced the name *Streptococcus hemolyticus* which has enjoyed considerable popularity. He did not state the sources of his strains nor did he report other characteristics than the appearances produced on blood agar plates. As a proper name *Streptococcus hemolyticus* has neither priority nor the historical definition of *Streptococcus pyogenes*. Some more recent authors have used *Strepto-*

coccus hemolyticus as synonymous with *Streptococcus pyogenes* while others apparently mean only a hemolytic streptococcus. The former should revert to the valid name; the latter should avoid the use of any proper name. Medical literature suffers much from such reports as Streptococcus hemolyticus Infection Successfully (or Unsuccessfully) Treated with Sulfonamides and advertisements of disinfectants which are claimed to kill *Streptococcus hemolyticus* within 1 minute. Which hemolytic streptococcus? Some are sensitive to sulfonamides and some are not. Some are more easily killed by disinfectants and heat than others.

Other hemolytic streptococci than *Streptococcus pyogenes*, some of them belonging to serologic Group A, are less frequently isolated from human infections. *Streptococcus infrequens*, as named by Holman¹⁴ (1916), was a hemolytic streptococcus which fermented lactose, mannitol and salicin. Holman listed 29 strains from human sources. By the same definition, but adding positive fermentation of trehalose and sorbitol, Frost and Engelbrecht¹² (1940) reported 828 strains from milk and 76 strains from throats of dairy employees. The sources of Holman's strains make it possible that they might have belonged to either serologic Groups A or D. The strains of Frost and Engelbrecht might have belonged to Groups D or E, the fermentation of sorbitol, making probable the exclusion of those of Group A. From autopsies at the Johns Hopkins Hospital during six years (1932-1938) there were isolated 33 strains of beta hemolytic streptococci which fermented lactose, mannitol, salicin, trehalose and sorbitol; these probably belonging to Group D. Seven other strains differed in not fermenting sorbitol; these, in the light of later experience, probably belonging to Group A. During the next 5 years (1938-1943) serologic groupings of all beta hemolytic streptococci was carried out. In this period 40 strains, fermenting the 5 carbohydrates, were isolated; all belonging to Group D. Two other strains, differing in not fermenting sorbitol, were of Group A. This would indicate the probability that most of Holman's strains, also from human sources, were of Group D rather than Group A. The beta hemolytic streptococci of Group D have been adequately described by Sherman²¹ (1937). Since Holman may have had one or more Group A strains among those which he described, *Streptococcus infrequens* Holman¹⁴ 1916, *em.* Brown⁵ 1939 may be emended to include only those beta hemolytic streptococci of Group A which ferment lactose, mannitol, salicin and trehalose but not sorbitol. Of the 9 strains mentioned above, isolated in this laboratory, 5 were from lungs, 2 from bronchi and 2 from heart blood.

Streptococcus erysipelatos was named by Rosenbach²⁰ (1884) although he gives credit for its discovery to Fehleisen¹¹ (1883). Rosenbach regarded *Streptococcus erysipelatos* as different from *Streptococcus pyogenes*, principally on the basis of minute colonial differences, but most authors have come to regard them as identical. Birkhaug³ (1925) and Tunnicliff²⁴ (1926) consider *Streptococcus erysipelatis* a distinct species. Evans and Verder¹⁰ (1938) found that some of Birkhaug's strains were of Group C, whereas erysipelas strains from other sources were of Group A. Since the strains of Fehleisen and Rosenbach cannot be identified, the name *Streptococcus erysipelatos* (or *erysipelatis*) should not be used without exact descriptive emendation.

Streptococcus scarlatinæ Klein¹⁵ (1887) was applied to streptococci derived from cases of scarlet fever in England. Gordon¹³ (1903-1907) and Andrewes and Horder¹ (1906) found that most of their scarlet fever strains fell into 2 fermentative groups, those which fermented salicin and

those which did not. Taking into consideration their hemolytic character, Andrewes and Horder regarded the former as *Streptococcus pyogenes* and named the latter *Streptococcus anginosus*, n. sp. Other differences (cultural, serologic and phageologic) also indicate that the salicin fermenting and non-fermenting streptococci from scarlet fever cases can hardly be regarded as of 1 species (Williams²⁵ 1932, Evans⁹ 1937, Sherman²¹ 1937). The question is further complicated by the existence of 2 serologic groups (A and G) among strains of *Streptococcus anginosus* Andrewes and Horder. The strains from scarlet fever apparently belong to Group A, while some from other sources belong to Group G. Obviously, the reasons which led Andrewes and Horder to reject the name *Streptococcus scarlatinæ* (*nomen ambiguum* or *nomen confusum*) would argue for the rejection of *Streptococcus anginosus*. The only way to conserve these names is to emend them in the light of recent discoveries. Evans⁹ (1937) has proposed to do this for the salicin negative, scarlet fever strains of Group A and, if one follows her, the name should be *Streptococcus scarlatinæ* Klein¹⁵ 1887, *cm.* Evans⁹ 1937. Since this would remove such strains from *Streptococcus anginosus* Andrewes and Horder¹ 1906, it would seem in order to confine the name *Streptococcus anginosus* to certain streptococci of Group G as suggested by Sherman²¹ (1937). In any event, it must be borne in mind that *Streptococcus scarlatinæ* Klein¹⁵ 1887, *cm.* Evans⁹ 1937 is not the streptococcus of scarlet fever but is a streptococcus of scarlet fever.

Streptococcus alactosus Brown⁴ 1919, *cm.* 1939 is a beta hemolytic streptococcus of Group A which ferments mannitol, salicin and trehalose but does not ferment lactose nor sorbitol. It liquefies human fibrin and does not hydrolyze sodium hippurate. The first strains, described by Smith and Brown²² (1915), were from an institutional outbreak of sore throat in 1913; 2 of the strains from peritoneal pus and 2 from throats. Immune serum prepared against one of these strains agglutinated the others to high titer and did not agglutinate strains of *Streptococcus pyogenes* (*epidemicus*). Although this outbreak was described along with other "presumably milk-borne epidemics," there was no evidence that it was milk-borne. The streptococcus was not found in samples of milk from 25 cows supplying milk to the institution. So far as I know, this streptococcus has never been found in other than human pathologic material, and very rarely in that. During a period of 5 years it has been isolated twice from lungs at autopsy; both cases of lobular pneumonia following upper respiratory infections. One of the cases had been treated with sulfanilamide without satisfactory response. Under the name "*Streptococcus hemolyticus* II," Holman¹⁴ (1916) reported 1 other strain of a hemolytic streptococcus which fermented mannitol and salicin but not lactose. It was from an abscess of the chest wall.

Conclusion. Named as emended above, 4 species of beta hemolytic streptococci of Lancefield's serologic Group A may be distinguished. They are as listed in Table 1.

It is realized that the relative prevalence might be quite different in material from other sources, *e. g.*, normal throats, intestines or the genito-urinary tract, or in material taken at different times or in other localities.

It might be convenient to regard species II, III and IV as "variants" of *Streptococcus pyogenes*, but is there any justification for it and would it be informative to have them so reported? If, as is commonly recognized by geneticists, variation in the direction of loss of characters is much more common than is the acquirement of characters, perhaps *Streptococcus infrequens* should be regarded as the parent species. Its infrequency is

no argument for or against its systematic significance; specimens of "missing links" may be rare. Although there may be experimental evidence that, after unusual treatment or prolonged selection, variation with respect to carbohydrate fermentation may occur, the fact remains that cultures of these species have been preserved for many years without evidence of variation. Furthermore, if variation occurs, it is important to recognize the variants; they may present differences in pathogenicity or in susceptibility to drug treatment. Only by the slow accumulation of exact records can these problems be solved. Our plea is less for correct nomenclature, desirable though it is, than for exact nomenclature. Opinions may differ regarding the former, but not the latter.

TABLE 1

	Dextrose (final pH)	Lact.	Mann.	Sal.	Treh.	Sorb.	Prevalence* at J. H. Hosp.
I. <i>S. pyogenes</i>	5.0 ±	+	—	+	+	—	83 strains
II. <i>S. infrequens</i>	5.0 ±	+	+	+	+	—	2 "
III. <i>S. scarlatinae</i>	5.0 ±	+	—	—	+	—	3 "
IV. <i>S. alacidosus</i>	5.0 ±	—	+	+	+	—	2 "

All 4 species are fibrinolytic for human fibrin and fail to hydrolyze sodium hippurate.

* Prevalence among 203 strains of beta-hemolytic streptococci isolated from autopsies at The Johns Hopkins Hospital during a 5 year period.

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PREVENTIVE MEDICINE AND EPIDEMIOLOGY

UNDER THE CHARGE OF

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VITAMIN DEFICIENCY AS AN EPIDEMIOLOGIC PRINCIPLE

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IMMUNITY resulting from previous exposure to the infectious agent has long held first place in studies which seek an explanation for resistance

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to infectious disease. It is clear that immunity from a previous infection, in measles, for example, affords resistance to subsequent infection. In other diseases, where some or even the majority of individuals, even though infected, never develop clinical disease, a favorite explanation has been subclinical immunity from "repeated bombardment with small subinfective doses." It has now become clear that in many diseases, other forms of resistance independent of antigen-antibody mechanisms play a major rôle.

Amongst the numerous hypotheses which have been considered to explain the inborn or acquired, constitutional or environmental, temporary or permanent, autarceologic resistance, faulty nutrition has become a generality.

"Clinicians generally agree that a deficiency in vitamins or other essential food elements usually results in a lowered natural resistance to bacterial infections," begins a recent editorial,²² the occasion for which was the clear-cut experimental demonstration that a number of vitamin deficiencies as well as dietary depletion have the opposite effect—a marked increase in natural resistance to several virus infections.

The idea of dietary deficiency as a factor in resistance to infection seems to have for its foundation, first, the long association between famine and pestilence; and, second, the distinct association between vitamin A deficiency and xerophthalmia (not an infectious process itself, but frequently followed by secondary infection).

Famine and Disease. Countless references to famine are coupled with the phrase "followed by a plague or pestilence." One of the earliest notes occurred in 503 to 443 B.C. in India. "During the reign of the Emperor Tci-chund, extending over this period, there was a great pestilence and famine." Every century had at least one note of famine and plague, even through the 19th century. From 1193 to 1196 in England and France, famine was occasioned by incessant rains, and "the common people perished everywhere for lack of food, and in the footsteps of famine the fiercest pestilence followed, in the form of an acute fever." In 1600 in Russia—"famine and plague, of which 500,000 died," and so on.¹¹⁵

In many accounts of famines, the association between famine and fever, especially typhus, has been remarkable. Hirsch⁴⁵ observed "the coincidence in time between epidemics of typhus and the state of want brought about by failure of the crops, commercial crisis, war, and other far-reaching calamities." Chronicles of the pestilences of war and famine almost invariably included typhus fever as an immediate sequel to these disasters. Bateman³ is credited with being the first to give definite expression to the opinion "that deficiency of nutriment is the principal cause of epidemic fever." "Famine and fever as cause and effect" was the title of an essay by Corrigan¹⁶ following the Irish famine in 1846, and the idea of "hunger typhus" became more prevalent. It was a common observation that typhus appeared among the poor in proportion to the degree of want they had suffered. During the Irish potato famine those people who had had insufficient food were most frequently attacked, and this selection seemed to support the idea of infectious disease being directly dependent on lack of food.

These older concepts have survived to the present day; as, for example, in the observations of Zinsser, Castaneda and Seastone,¹¹⁸ who found that guinea pigs and rats, subjected to vitamin-deficient diets to a point at which deficiency symptoms appeared and then inoculated with typhus virus, exhibited clinical pictures indicating a far more severe infection than that observed in normal animals after inoculation. There was also

a wider distribution of *Rickettsiæ* and a concentration of organisms that, in pleural and peritoneal exudates, amounted to almost cultural proportions. They remarked, "From the epidemiological point of view these experiments at least suggest an explanation of one of the important factors which enter into the historical association of high typhus mortality with war and famine."

Numerous other observers have attempted to place famine correctly as merely an indirect cause of epidemics of typhus, pointing out such other influences as overcrowding and lack of cleanliness. Several also have insisted that epidemics of typhus had frequently occurred in regions where there was no question of famine; and that at other times great famines were not followed by typhus. Ireland had suffered many famines, while typhus in epidemic proportions appeared in only a few of them.

This concept of the secondary rôle of famine in disease has been recently developed by Sigerist⁸⁶ who has supplied a logical sequence of events. During a time of famine, living conditions became poorer. Lice were more prevalent and once typhus started, it spread rapidly. Water supplies may have been neglected, what little food remained was not well controlled, and epidemics of cholera and dysenteric diseases resulted. Epidemics of plague often started following a drought that caused a crop failure. Rats moved closer to man to obtain food and, if plague was present, the disease was likely to be passed on to man. The same occurred following floods in which the crops, standing or harvested, were spoiled, and the rodents joined man to share in what food there was available.

Xerophthalmia. Severe deficiency of vitamin A with resultant xerophthalmia is almost unknown in the United States, and is common only in restricted areas in India and China. The loss of resistance to infections of various kinds in patients with xerophthalmia has been cited as a characteristic of this disease. Most reports show that a marked deficiency is associated with more numerous and severe infections. In 165 cases Blegvad⁷ found 210 complications: pneumonia, bronchitis, otitis media, and so on. His cases undoubtedly suffered from a marked vitamin A deficiency, since they were clinical cases of xerophthalmia, but other deficiencies that very probably were present were not taken into consideration. Of Bloch's¹⁰ group of 86 children with keratomalacia, 80% had infections of the respiratory tract, ear, urinary tract, or skin. He compared this group of patients with vitamin A deficiency with a group of 32 cases with scurvy. In the latter there were only 30% with infections. Only one case of pneumonia was present, in a patient with vitamin C deficiency who also had xerophthalmia. The other infections in the group of patients with scurvy, mainly mild catarrhal, cleared rapidly. Infections in the patients with vitamin A deficiency were not only more frequent but also more severe than those in the patients with vitamin C deficiency. Other^{8,9} reports of small numbers of cases stressed the finding of the large percentage of infections seen in patients with vitamin A deficiency.

Spence,⁸⁹ on the other hand, found no increase in systemic infections in 17 cases of xerophthalmia studied over a period of 12 months. The 3 older patients had only the complaint of night-blindness, but the others had xerosis conjunctivæ, Bitot's spots, or commencing keratomalacia. The general health of the families of the 11 youngest patients had not apparently changed; the incidence of infection was not increased and lowered resistance was not indicated. A high incidence of skin sepsis, impetigo, and boils was present in 99 people examined in the families of these patients, but no increase in systemic infections.

In experimental studies of marked vitamin A deficiency and the resultant xerophthalmia without particular reference to concurrent infection, Emmett²⁶ found that, of 122 rats on low vitamin A diets, 98.2% developed xerophthalmia; and in Osborne and Mendel's⁶⁹ experiments using 136 animals on vitamin A free diets, only 69 (approximately 50%) developed the disease. This raised the question of possible variation in susceptibility in the several strains of animals. These experiments were performed primarily to show that xerophthalmia was not due to infection, but was a result of vitamin A deficiency.

Anti-infective Vitamin. The idea that vitamin A has properties that will increase resistance to infection has led to its being popularly called the "anti-infective" vitamin. It has been advocated especially by producers of vitamin products for the prevention of the common cold and similar infections. In 1935, the Council on Pharmacy and Chemistry of the American Medical Association defined its attitude toward the permissible claims which advertisers may make for vitamin A in cod-liver oil: "By virtue of its vitamin A content it promotes growth and, as indicated by experimental studies, may be an aid toward the establishment of resistance of the body to infection in general, though it has not been shown to be specific in the prevention of colds, influenza, and other such infections."⁵⁹

Wolbach and Howe¹¹³ in 1925 noted that the normal columnar epithelium of the nasal mucosa, trachea, etc., was replaced in vitamin A- and D-deficient animals by stratified keratinizing epithelium. Several factors were suggested as causes for increased susceptibility to infection. The reduction or absence of mucous membrane secretions that wash off bacteria and small epithelial particles would impair this mechanical action. Epithelial debris, especially in glands with blocked ducts, would provide a good medium for bacterial growth. The eye changes seen in acute vitamin A deficiency were considered due, at least in part, to infection on the grounds that resistance was impaired by vitamin A deficiency. However, from their work, Wolbach and Howe concluded that the substitution of keratinizing epithelium was not secondary to infection and that it probably was a primary effect due to withdrawal of factors necessary for the maintenance of differentiation of epithelium. The possibility that keratinization was secondary to the effects of vitamin deficiency on the metabolism of tissue was considered also. Mori⁶⁶ also had reported changes of the mucosa in rats deficient in fat-soluble vitamin A.

Cramer and Kingsbury²⁰ had concluded that a diet deficient in vitamin A impaired the efficiency of the local tissue defenses but did not apparently diminish the efficiency of the general defenses.

The loss of the protective powers of the epithelium due to diminished or absent mucus secretion and loss of ciliary motion was listed as one of the important predisposing factors to infection by Blackfan and Wolbach.⁶

Green and Mellanby³⁵ reported that young rats fed on diets rich in all known factors except vitamin A invariably died of some infective condition, especially local infections such as abscess at the base of the tongue, bronchopneumonia, infection of the genito-urinary tract, middle ear infection or similar lesions. The animals, unless too ill when treated, were cured by vitamin A. The results were so impressive and the specificity of the vitamin seemed so apparent that they called vitamin A the anti-infective vitamin. Mellanby⁶² observed an epidemic of bronchopneumonia in his experimental puppies on a diet deficient in vitamin A, and found that the condition did not occur when cod-liver oil or butter was given to the animals. Vitamin A appeared to increase the resistance of the puppies

to bronchopneumonia. Two views of the mechanism of production of this increased resistance were taken: that the epithelial tissues were maintained in a normal condition by the fat-soluble vitamin and became hyperplastic and metaplastic and more susceptible to bacterial infection when they were absent; or that a local infection following vitamin deficiency caused hyperplasia of the epithelium. Mellanby and Green *et al.*^{36,63} also studied the effect of vitamin A on puerperal septicemia with favorable results in the first cases. Later investigation did not show this benefit.

Rats were placed on diets low in fat-soluble vitamin A but adequate in other food elements in an experiment by Daniels, Armstrong, and Hutton²¹ (16 test rats and 29 controls were used). The test rats were killed at varying intervals and the heads examined with special attention to the nasal mucosa. In all of the experimental rats, the nasal mucosa was covered with thick creamy exudate. The middle ears of 6 were examined, all of which were filled with pus; 3 had abscesses at the base of the tongue. Two rats after 9 and 11 weeks on the vitamin A-deficient diet were given cod-liver oil for 2 weeks, and then were killed and examined. Both of these had pus on the nasal mucosa and in the middle ears. One rat killed after 4 weeks on low vitamin A showed no inflammation of the nasal mucosa, while 2 others after 6 and 8 weeks on the deficient diet had marked nasal inflammation, and 1 also had pus in the middle ear and an abscess at the base of the tongue. Of the 29 controls, only 5 showed a little reddening of the nasal mucosa and no exudate, middle ear infection or abscesses at the base of the tongue. They concluded from their findings that fat-soluble vitamin A plays an important rôle in immunity to pyogenic infections, and that a general breakdown following diets low in the fat-soluble vitamin is secondary to this infection. Bacterial invasion of the mucous membranes of the nasal cavities and ear seemed to advance more easily when the diet was deficient. It has been assumed that some fats, especially cod-liver oil, have a beneficial effect in tuberculosis and some other infections, and the authors believed that the findings of this experiment seemed to provide evidence in support of these clinical observations.

McCollum⁵⁸ early described infection present in rats on a diet free from fat-soluble vitamin A.

Hess, McCann, and Pappenheimer,⁴⁴ Goldblatt and Benichok,³⁴ Turner,¹⁰⁰ Sherman and Burtis,⁸³ Macy and Outhouse,⁵⁶ Harris *et al.*⁴¹ all found a high percentage of incidental infections in rats receiving a diet deficient in vitamin A.

Turner and associates^{85,101} reported Gram-negative cocci present in the upper respiratory tracts and middle ears of rats suffering from lack of vitamin A. They were shown more frequently in the animals that showed the most severe symptoms of vitamin A deficiency. Tyson and Smith¹⁰² noted infection always present even in the earliest stages of vitamin A deficiency and in late cases it was the predominant feature.

Torrance⁹⁷ found that feeding increased amounts of vitamin A to guinea pigs did not increase their survival time after injection of diphtheria toxin. Vitamin A assay of the livers brought out the fact that cod-liver oil had not increased the vitamin A storage. Later investigations,⁹⁸ using tetanus toxin, did not establish a correlation between the amount of vitamin A in the livers of guinea pigs injected with bacterial toxin and their length of survival time. The livers of animals from which bacteria were recovered at autopsy showed a lower level of vitamin A than in the livers of the guinea pigs that contained no organisms.

The amount of vitamin A in the human liver has been determined by

several workers (Laqueur, Wolff, and Dingemanse,⁵³ Wolff,¹¹⁴ and Moore⁶⁵). They found low values of vitamin A present generally in the livers of persons who have died from infections, but a rather wide range was seen in any infection or disease. The possibility that vitamin A stores are depleted from underfeeding or by infection should be considered. A decrease in blood carotene and vitamin A has been found by McCoord and Clausen.^{60,104}

A great number of experiments with various organisms and using several techniques have been reported. McClung and Winters⁵⁷ found a marked increase in susceptibility to infection with *Salmonella enteritidis* injected intraperitoneally in a group of rats on a vitamin A-free diet for 7 weeks. Lassen⁵⁴ using vitamin A-deficient rats inoculated by mouth and subcutaneously with paratyphoid, reported a marked decrease in resistance of these animals as compared to rats on adequate diets. Vitamin A-deficient rats injected intraperitoneally with a bacillus of the mucosus capsulatus group in Boynton and Bradford's¹² study showed markedly decreased resistance to the infection but no increased susceptibility in rats on a vitamin D-deficient diet. Spindler,⁹⁰ infecting rats with *Nippostrongylus muris* and repeating the infection later, found that the animals deficient in vitamin A had had their resistance to superinfection markedly lowered. The effect of diet in epidemic infections in mice was studied by Topley, Greenwood, and Wilson.⁹⁶ They inoculated 25 mice with *B. ærtrycke*, put them into cages with 100 normal mice and observed them for 60 days. The addition of an excess of fat, butter or lard or a vitamin A concentrate seemed to produce an unfavorable reaction that was not shown when the mice were injected intraperitoneally. The addition of cabbage, carrots, or mangoes to an adequate diet did nothing to lessen the severity of the epidemic. They did not obtain any evidence that various additions to the diet increased resistance so as to produce a significant decrease in mortality under epidemic conditions.

Webster, in experiments the most striking result of which was success in the development of highly resistant or highly susceptible strains of mice to a given infection by selective inbreeding, tested the effect of nutrition on susceptibility. He found¹⁰⁹ that mice fed on a McCollum complete diet were more resistant to mouse typhoid, mercury bichloride intoxication and botulinus toxin than were similar mice fed on bread and pasteurized milk supplemented by an oatmeal and buckwheat mixture and dog biscuit. In Pritchett's experiments,⁷³ 5% butter fat or cod-liver oil added to a bread and milk diet appeared to increase the resistance of mice to *per os* infection with the paratyphoid mouse bacillus, but mice fed on a vitamin A-free fat diet showed no increased mortality as compared to those on a diet with cod-liver oil. In later experiments by Webster¹⁰⁸ with epidemics in mice he used variations from adequate to optimum constituents in the diet as one method of controlling the amount and severity of infection.

Greene³⁷ reported spontaneous infections with *B. pyocyaneus* in vitamin A-deficient rabbits and greater susceptibility to intravenous infection with Type 1 pneumococcus in these deficient animals than in normal controls. The vitamin A-deficient rabbits were more susceptible to intranasal infection with *B. lepi-septicum* than control animals.

Microscopic lesions were reported in 100% of vitamin A-deficient rats by Gross,³⁸ although no clinical signs had been noted. Hou⁴⁸ also observed a high incidence of spontaneous infection in rats on vitamin A-deficient diets.

Rats and rabbits, suffering from lack of vitamin A, became less resistant to infection with the anthrax bacillus and the pneumococcus; but, as Werkman¹¹⁰ pointed out, rats suffering from lack of vitamin B likewise were more susceptible to these infections, but since starvation also decreased their resistance, these results were not specifically due to vitamin A deficiency.

Evidence that there has been a visible decrease in morbidity statistics since the discovery and mass production and ingestion of vitamins is lacking. As Simmonds⁸⁷ has stated, "With the possible exception of pellagra, clear-cut clinically defined disease entities of dietary origin have not played a large part in mortality and morbidity statistics."

To summarize the results of investigations, indications are that vitamin A prevents a type of keratinization of tissues that is produced by deficiency of vitamin A, and reduces the possibility of secondary infection. In this way it might be termed "anti-infective" but there apparently is no effect on general immunity; and its therapeutic use in specific infections, *unless an actual deficiency is present*, has not been justified. The question of the influence of vitamin A on the epithelial tissues of the lung in pneumonia when there is a deficiency is controversial. Thus the evidence at present shows that vitamin A is not the only or most important factor in prevention of infection. "Anti-infective" vitamin with its present implications is a term which as yet does not appear to be justified.

One critic,⁴⁰ himself a nutritionist, sums up the situation in the following homely style, "Today vitamin A is often spoken of as the 'anti-infective vitamin,' and it is suggested that if you take enough of it it will prevent your catching coughs and colds, and the commoner infectious diseases, such as measles, chickenpox, or scarlet fever, etc. It is even claimed (as you will have noticed if you read the advertisements) that should you have already caught one of these infectious diseases a dose of vitamin A will help you to recover quickly."

"How did this theory start? Well, it was known that animals dying from vitamin-A deficiency became infected, and it was assumed rather too easily that a kind of generalized converse was true also, that is, that 'infections are due to vitamin-A deficiency.' The logic of course is at fault, and the theory also in my opinion is at variance with the known facts. . . . The position therefore in a nutshell is this. If you take insufficient vitamin A, you are certainly liable to develop special kinds of localized infections. It is wise, therefore, to take care that your diet is adequate and well-balanced. But this has nothing to do with ordinary infectious diseases as commonly met with; and in any case most people in this country do appear to get ample vitamin A, so that in such circumstances it seems futile to try and treat ordinary infectious diseases and septicæmias with vitamin-A medication."

Vitamin B deficiency and susceptibility to several infections have been studied by many workers. Badger, Masunaga, and Wolf¹ obtained evidence that rats on a thiamin-deficient diet were more susceptible to rat leprosy than were normal rats. Rose and Rose⁷⁸ injected dogs partially deficient in vitamin B with *Staph. aureus*. They found that they appeared more susceptible to deleterious effects of artificial infections with *Staph. aureus* and the survivors had positive blood cultures longer than the controls. Pemberton and Bessey⁷⁰ reported that riboflavin-deficient rats showed loss of resistance to murine typhus. Rats on a vitamin B complex-free diet and infected with an enteritidis organism had 19% survivors as compared to 75% survivors with brewers yeast added to their diet in an

experiment by Ross and Robertson.⁷⁹ Rats on a diet deficient in either riboflavin or thiamin and infected with *Nippostrongylus muris* showed a marked reduction in resistance in Watt's work.¹⁰⁶

Wooley and Sebrell¹¹⁶ reported that mice deficient in riboflavin or thiamin were more susceptible to a fatal infection with pneumococcus Type 1 inoculated intranasally than mice on an adequate diet. They carried out paired feeding experiments to show that this increased susceptibility was not due to a restricted food intake. Large amounts of riboflavin or thiamin given at the time of inoculation did not reduce mortality in the deficient group.

A life-long deficiency of vitamin B₁ in rats resulted in a shortened duration of life and decreased reproduction in a study by Drummond and associates.²⁴ The incidence and severity of chronic lung infections, as well as other disorders and tumors was not influenced by the vitamin deficiency.

Increased resistance to ulcerative cecitis of rats on a diet deficient in the vitamin B complex was observed by Bloomfield and Lew.¹¹ The controls on a normal diet had an incidence of 50% of cecitis and the animals deficient in the B complex showed insignificant lesions in 19%. The cause of cecitis is questionable, many of its features suggesting a virus disease.

Vitamin C-deficient diets have been shown to increase the susceptibility of guinea pigs to various infections. Theobald Smith⁸⁸ noted pneumococcus pneumonia in his guinea pigs, which was controlled by adding green fodder to the diet. Findlay²⁷ reported that guinea pigs fed on a diet deficient in vitamin C succumbed to a smaller infecting dose of the pneumococcus, *Staph. aureus*, *Strep. hemolyticus*, and *B. coli*, and Werkman, Nelson, and Fulmer¹¹¹ found that vitamin C-deficient guinea pigs revealed a definite though not marked break in resistance to infection by the pneumococcus and *B. anthracis*, but no difference in their ability to produce specific agglutinins for the typhoid bacillus as compared with healthy animals. Markedly scorbutic guinea pigs showed a drop in resistance to *B. necrophorum* in McCullough's⁶¹ experiment. Avirulent human strains produced minor abscesses in these deficient guinea pigs although no reaction was evident in animals on adequate vitamin C diets. McCullough noted that a severe scorbutus was necessary before a drop in resistance became evident. Chronic subscorvy with a superimposed Beta hemolytic streptococcus infection that produced an arthropathy similar to that of rheumatic fever and rheumatoid arthritis was reported by Rinehart, Connor and Mettier.^{75,76} They suggested that a subclinical degree of scurvy may make up the rheumatic tendency which, with an added factor of infection, causes the development of rheumatic fever or rheumatoid arthritis.

The addition of vitamin C and other vitamins to the diets of children with rheumatic fever did not reduce the incidence of upper respiratory infections, and there has been no correlation between rheumatic fever and scurvy.⁶¹ In tuberculosis⁷² and some other infections, more ascorbic acid than average apparently is needed to maintain a high plasma level; however, there is no evidence that a deficiency of vitamin C causes susceptibility to infection. Pijoan and Lozner⁷¹ recently have concluded that ascorbic acid has but two known uses: the prevention and the treatment of scurvy. Any other use of vitamin C in man lacks controlled experimental justification.

The addition of vitamin D to a diet rachitogenic but otherwise adequate, raised the resistance of rats to a "rat typhoid" infection fed by mouth in

an experiment by Robertson and Ross.⁷⁷ Greene³⁷ showed that more susceptibility to intranasal inoculation with *B. lepi-septicum* was present in vitamin D-deficient rabbits, and a higher morbidity and mortality following intranasal inoculation with Type 1 pneumococcus than controls. Nonetheless, from these beginnings which, as has been pointed out, are in many respects tenuous or at least "highly experimental," the idea of vitamin deficiency is at the back of many of our troubles with infectious disease.

Factors that have contributed to the expansion of this idea are undoubtedly in the first place, the elucidation of vitamin deficiency as the cause of a number of non-infectious diseases: rickets, scurvy, beri-beri, and pellagra; and second, advancement in knowledge of the chemical nature of vitamins which has made possible their production and sale in seemingly unlimited quantity.

It should be noted here that all the non-infectious diseases due to vitamin deficiencies, when viewed epidemiologically, follow limited patterns of distribution which in themselves bespeak vitamin deficiency, and show a complete correspondence with demonstrated patterns of vitamin deficiency. Nevertheless, the lack of association between the distribution of any of the infectious diseases and known vitamin deficiency has not seemed to interfere in the least with generalizations drawn almost exclusively from laboratory experiments in which animals subjected to the severest vitamin deficiencies have been shown to vary in their resistance to infection. Watson¹⁰⁷ summed up the situation briefly, "The available evidence, taken as a whole, would seem to suggest that vitamins B and D have little, if any influence on resistance, while in the case of vitamin C, the observations recorded are particularly confusing and difficult to interpret."

Another factor that adds to the confusion is the interpretation of reported favorable therapeutic effects of various vitamins in a number of infectious diseases as an indication that the converse—vitamin deficiency—was responsible for the disease.

For example, good results from vitamin A therapy in treatment of measles were reported by Ellison.²⁵ He divided 600 cases of measles into 2 equal groups, one of which received the regular diet supplied to measles cases and cod-liver oil during convalescence, and the other received as supplement from the day of admission a concentrate containing 300 Carr and Price units of vitamin A and 2000 international units of vitamin D, the equivalent of approximately 1 oz. high grade cod-liver oil. This supplementary vitamin was continued for from 7 days to 3 weeks. He found that, of the treated 300 cases, there were 11 deaths (3.7%), and of the untreated cases there were 26 deaths (8.7%), a difference of 2.5 times the standard error, or 3.7 times the probable error. On the other hand, Mackay⁵⁵ and associates found no favorable results in studies apparently better controlled.

Sutcliffe, Place and Segool⁹² treated a series of 509 cases of scarlet fever for 10 days after admission with a total of 400,000 U.S.P. units of vitamin A. The incidence of otitis media in this series was 9.4% as compared to 11.3% in 343 cases which were not treated with cod-liver oil. They found its prophylactic use apparently was without effect on the liability of scarlet fever patients, none of whom suffered from clinical deficiencies, to develop otitis media. Clausen¹⁵ agreed with the idea that there was no obvious benefit from administration of carotene during scarlet fever and

was inclined to think that his cases did not suffer from a deficiency of vitamin A so no benefit should have been expected.

The effect of vitamin A on the course or incidence of other infections in man has been investigated, but vitamin-A deficiency was not shown before the studies began. Donaldson and Tasker²³ believed that a favorable effect on the outcome in pneumonia was obtained from the administration of vitamin A. Orenstein,⁶⁸ however, in the treatment of pneumonia in South African native mine employees, found that 375 cases treated with vitamin A and 389 cases acting as controls had almost identical case mortality, complications, lung involvement, and so on. He reported no benefit from this type of therapy.

The expansion of the idea of vitamin deficiency and susceptibility to infection has now extended into the realm of general popularity. In spite of the fact that the adequacy of the use of natural foods rather than vitamin pills and capsules have been repeatedly stressed by nutritionists, the drug store, rather than the grocery store, has become the dispensary for vitamin preparations in all sorts of combinations recommended for perhaps chiefly the prevention of the common cold, and now, in view of the stress on keeping fit during the emergency, for the maintenance of defense work at highest pitch.

The high pitch of vitamin popularity is well portrayed by an article in the section on Medicine and the War under the title, "Nation Faces Vitamin A Deficit."⁶⁷ In this item the Fish and Wildlife Service of the Department of the Interior recently warned that the nation faces a vitamin A deficit, that the chief source of vitamin A in the United States, the soupfin shark fishery, apparently is being rapidly depleted. It was pointed out that landings in February, 1944 were 70% below those of February, 1943, although fishermen had intensified their efforts. At the center of the fishery, landings for February, 1944 were about one-third those of the corresponding month of 1943. The Fish and Wildlife Service announced that vitamin A stock held by producers and pharmaceutical houses at the end of February, 1944 totaled approximately 51 trillion units as compared to 88 trillion units at the end of February, 1943. They stated that indications are that consumption of vitamin A in the United States now exceeds production.

Two major factors working in combination seem to have contributed to the wholesale consumption of supplementary vitamins which has outdistanced the development of any scientific basis for their use. One of these has been the development of knowledge of the chemical nature of vitamins, which has made possible their manufacture and sale direct to the public through modern advertising. For instance, at a drug store counter recently, a person whose general appearance indicated an economic and intelligence status which made one feel that she needed a good selection of food, was heard to ask for a particular pharmaceutical preparation containing so many units of this and that vitamin with addition of one or two of the other vitamins, using their correct chemical names—all in terms which compared favorably with those used by the most elaborate prescription writer in the days when *materia medica* was a pivot on which Medicine revolved.

The other has been the tendency of medicine itself to "try" this new line of pharmaceuticals for the many conditions encountered for which it has no satisfactory remedy.

Vitamin Deficiency and Virus Infections. Attempts to show that certain vitamins increase resistance of the animal to various virus infections

have generally been completely unsuccessful. In several instances it has been shown that susceptibility to these infections actually has been decreased. This resistance to virus disease might be said to have been noted indirectly by Underwood¹⁰⁸ as early as 1789 when he observed that poliomyelitis attacked the finest children. In Rous's⁸⁰ work, fowls sick from an intercurrent disease, characterized by rhinitis, conjunctivitis and marked depression and emaciation, were less susceptible to the sarcoma virus than healthy ones. The sarcoma nodule may cease to grow and even regress during the period of illness in the host, and with return of health the tumor may reappear and grow.

Marsh-Buffalo mice inoculated with sarcoma 180 were maintained on a synthetic diet containing vitamins of the B group except B₆.⁵ The rate of tumor growth showed a marked and significant drop when B₆ was deficient. When vitamin B₆ was added to the diet without other change or increase in the caloric content, the rate of tumor growth increased. There was increased rate of growth on a diet completely deficient in B complex but with vitamin B₆ added. Pantothenic acid deficiency had no effect on the rate of tumor growth in these experiments.

Underfeeding appeared to affect the initiation and growth of tumors differently.⁹³ Fewer tumors were formed in underfed mice and they were initiated at a later time. The rate of growth was about the same in underfed as in full-fed animals. When previously full-fed animals were subsequently underfed, the rate of growth of the tumors diminished. In determining the cause of retardation of initiation and growth of tumors, the possibility of restricted metabolism and growth of the animals, whether produced by underfeeding or an interference with utilization, must be considered.

When rabbits were deprived of food and injected with vaccinia, the lesions were fewer or smaller. If the animals were allowed to drink water, thus increasing the amount of interstitial fluid, the lesions were even fewer. The lesions were more numerous if the interstitial tissues were dehydrated.⁹¹

In experiments by Langenbeck and Enderling⁵² with foot-and-mouth virus, no protection was reported from vitamins A, B₁, B₂, C, or D in the guinea pig.

Cowdry, Lucas, and Neff¹⁸ in experiments with a total of 70 B₁-deficient and 43 B₂-deficient rats found that the rats deficient in these vitamins showed slightly more deaths than do normal rats when injected intracerebrally with herpes virus. They did not consider the evidence sufficient to show that resistance to herpes was actually reduced by these deficiencies.

Jungeblut⁵⁰ reported a definite decrease in the percentage of animals developing paralysis when natural vitamin C therapy was used in experimental poliomyelitis. Sabin⁸¹ found no difference in the appearance of paralysis in monkeys deficient in vitamin C as compared to those who had had adequate amounts. The number of experimental animals was small: only 12 animals out of 25 survived the preliminary vitamin C-deficient diet and could be used for the poliomyelitis experiment. There were 20 control animals on an adequate vitamin C diet. Of the total number—32—all but one developed paralysis; the one was in the untreated deficient control group.

Foster and associates,^{28,29,30,31} in experiments with mice on different levels of thiamin intake, reported the incidence of paralysis in mice injected with murine poliomyelitis virus (Lansing strain) on the high-thiamin diet to be several times that in mice on the thiamin-deficient diet.

In the average of their first 3 experiments, totaling 646 mice, mice on the low-thiamin diet had 13% paralysis as compared to 74% in mice on the high-thiamin diet. In a fourth experiment, the low-thiamin mice were given a maintenance level of thiamin, about 40% of the intake of the normally fed mice, to prevent their dying of deficiency for at least 21 days after inoculation, in which time paralysis would be most likely to develop. The low-thiamin group showed no increase in mortality as compared to the high-thiamin group. The incidence of paralysis in mice on the high-thiamin diet was several times that in the low-thiamin group, and paralysis was followed by death in a few days. The same workers made the interesting observation that a similar reduction in incidence of paralysis was produced by simple restriction of the stock diet; by restricting carbohydrate intake, paralysis and death were delayed.

A group of 35 mice on a thiamin-deficient diet and a group of controls at an optimum level were inoculated intracerebrally with Lansing mouse passage poliomyelitis virus in experiments by Rasmussen and associates.⁷⁴ None of the mice in the thiamin-deficient group showed paralytic symptoms by the 14th day, while 25 of the 35 mice on the optimal diet had developed paralysis. Inoculations with Theiler's virus were performed on mice in a similar experiment by these workers with riboflavin. Nine of the 26 in the deficient group developed paralysis, as compared to 16 out of 26 on an optimal amount and 15 out of 27 on a high-riboflavin allowance.

Ward, Sabin, Najjar, and Holt¹⁰⁵ found that children with paralytic poliomyelitis gave essentially the same results in thiamin excretion tests as those in normal children, suggesting that thiamin may not be a factor in determining whether paralysis will develop.

Toomey⁹⁴ reported experimental evidence that the ingestion of vitamin D protected monkeys from poliomyelitis when the virus is later given by way of the gastro-intestinal tract, and that the vitamin D-deficient animals were more susceptible to the disease when given by this route. He also presented evidence that the virus of poliomyelitis will spread along the nerves of vitamin D-deficient monkeys if virus is placed in contact with postganglionic fibers; poliomyelitis virus does not spread along the well-medullated nerves of healthy monkeys.⁹⁵ Results of studies by Sabin and associates⁸² were non-confirmative of Toomey's conclusions, and they found no evidence that the capacity of poliomyelitis virus to invade the central nervous system along peripheral nerves depended on vitamin A deficiency. Freshly passaged virus was used in Sabin's experiments and glycerinated M.V. in Toomey's work; the lower concentration of virus probably was a factor in the latter's experiments.

Cottingham and Mills¹⁷ have shown that vitamin deficiency severe enough to retard growth produces a corresponding reduction in phagocytic activity. In their work, the greatest phagocytic activity seemed to occur at levels of vitamin intake higher than those needed for good growth. They pointed out and emphasized¹⁶⁴ that low phagocytic activity was present with moderate vitamin deficiency, but it rose to normal when vitamin deficiency was severe. The work of Gellhorn and Dunn³³ seemed to bear out their results.

The Common Cold. Reports of experimental work on vitamin A and its effect on illness, especially colds, are conflicting. Most of the studies show that the incidence of colds was less, but controls generally were inadequate and volunteers were usually selected for the experiments.

The subjective element was eliminated in Cameron's¹³ study by giving the controls a placebo. The daily intake of vitamin A was calculated for

her subjects also. In this experiment the duration of colds was decreased by adding 5000 i. u. of vitamin A to a diet already containing 4300 i. u. daily, but the incidence of colds was not decreased.

Clausen^{14,15} discussed the limits of the anti-infective value of pro-vitamin A or carotene. From studies of the carotinoid pigment of the blood plasma in 1322 children after 2 years of age, he concluded that they generally received a diet adequate in vitamin A. Evidence that low intake of carotene was responsible for recurrent respiratory infections was not obtained. In his opinion, probably not more than 5 to 10% of these respiratory infections could be attributed to lack of carotene.

In several often-quoted experiments on human subjects, contradictory and rather questionable results were obtained. One group of young adult students were selected at random. They were divided into 3 groups: one received 200,000 i. u. vitamin A and 400 u. vitamin D per week; another received 400 u. vitamin D as viosterol; and the third group received maize oil. They were observed for over a year without evidence that supplemental vitamin A reduced the incidence of colds and without a significant difference in the frequency of other respiratory infections. Winter colds apparently were several days shorter when extra vitamin A was given.⁸⁴

Another investigation in 4 groups varying in size from 6 to 94 infants who were given small, moderate, large, and maximum amounts of vitamin A were observed for from 4 to 12 months without showing any significant difference in the incidence or severity of respiratory infections. The group receiving the largest amount of vitamin A had no more protection against respiratory infections than any of the other groups.²

Administration of vitamin A in the form of haliver oil or high-vitamin A foods to 50 school children divided into 2 groups and paired by age, sex, nutrition and history of susceptibility to colds showed a decrease in the incidence and severity of colds compared to a group of 25 control children who had a history of high resistance to colds. Improvement in the general health as shown by an increase in weight accompanied this increased resistance to colds. The results of this experiment are hardly conclusive, since there was involuntary selection for the various groups, as susceptible children were put into the groups to be given supplement, and other factors such as the general diets and intake of other food essentials were not considered.³²

In 162 medical students examined by Jeghers,⁴⁹ over one-third had low photometer readings and 12% had clinical manifestations of vitamin A deficiency. The incidence of colds in the subnormal group was approximately the same as that of the normal students, but they apparently were of longer duration.

Several other workers have carried out experiments on small groups of individuals in an attempt to show that vitamin A, in particular, is efficacious in preventing colds. Winholt and Jordan¹¹² showed little correlation in types of infant feeding and colds. Those with colds had a number of ailments other than colds, few of which illnesses were of infectious origin. Cramer¹⁹ refers to Dr. Curry Mann's report that boys supplied with an extra milk ration in a boys' school had an improvement in gains in weight and height and general health, and a "complete absence of illness." Wright, Frosst, Richel, and Lawrence¹¹⁷ gave 20 infants large amounts of vitamin A over a period of months, and as controls had 40 infants under the same conditions but given the amount of vitamin A

usually supplied in the group. No appreciable difference in the incidence of upper respiratory infections was found in the two groups.

Cod-liver oil supplied to workers in industry was reported to reduce colds, lost time, and hours of absence by Holmes, Pigott, Sawyer and Comstock.⁴⁷ One tablespoonful cod-liver oil daily was given to 185 from December to March inclusive, and 128 were used as controls. Of the workers receiving cod-liver oil, no colds developed in 55.1 %, as against 32.8 % in the controls. The cod-liver oil group lost time was reduced 51.9 %, as compared to 40.6 % in the controls. The average hours of absence were reduced from 20.4 in 1930 to 12.8 in 1931 in the cod-liver oil group, and in the controls increased from 17.4 to 25.1. Workers comparable in age, weight, sex, and type of work were selected for this experiment, but no control or record was made of the diet before or during the experiment.

Hess, Lewis and Barenberg⁴³ found no difference in the frequency of colds or the prevention of pneumonia and otitis media in 40 infants given large amounts of carotene daily, 40 given large amounts of haliver oil, and 80 no vitamin A supplement; all received viosterol. Infections of the skin, as impetigo, were present in the vitamin groups as often as in the control group.

The effect of vitamins on respiratory infections in infants was summed up by Hess.⁴² Vitamins A and D are not effective in increasing immunity to respiratory infection, while a lack of vitamin C may cause heightened susceptibility to infection of the respiratory tract.

In Beard's⁴ study, 36 first-year medical students were given cod-liver oil concentrate tablets daily and the incidence and severity of colds were recorded; 58.3 % showed a definite prophylactic effect compared to their colds in the previous year as determined from memory, 11.1 % a slight prophylactic effect, and 30.6 % no effect. During an influenza epidemic at the time, 56 % were attacked, approximately the same percentage that occurred in students not receiving cod-liver oil. In Tress'⁹⁹ paper a comparison was made between the incidence of colds in a test year and the year before. Two hundred and twenty-five children took halibut-liver oil regularly or irregularly. Of the ones taking it regularly, 78 % had fewer attacks. In a group of 76 children receiving cod-liver oil, 75 % of those taking it regularly had fewer colds.

Hoelzel⁴⁶ saw a parallelism between the incidence of colds and nutritional hydration from his personal experience. During fasting or marked under-nutrition colds did not develop, but appeared after periods when edema especially due to protein starvation was prominent. Keeping the hydration of the organism at a relatively low level, mainly by restricting carbohydrates and maintaining an adequate protein level may have prevented some colds. After excessive secretions were formed, bacteria then may have complicated the condition.

Summary. "Few investigators doubt that severe deficiency of vitamin A, or any vitamin, will lower resistance to infection, and almost all will agree that administration of vitamin A during the course of any infection will have little beneficial effect on the outcome unless a deficiency is present. Some workers believe that the frequency and high mortality rate in pneumonia of infants who are deficient in vitamin A result from a disturbance of function of the mucosa of all parts of the lungs. Others believe that administration of vitamin A in large amounts is beneficial in preventing common infections of the respiratory tract. This subject, however, is in general extremely controversial. Enough evidence

indicates that there are many other factors of equal or greater influence in infection than vitamin A and that there is no justification for calling vitamin A the 'anti-infection' vitamin."⁵⁹

In view of such a typical confusing statement, in a handbook of nutrition it should be pointed out that the science of nutrition itself (and science tends to be enthusiastic about its own wares) has by no means been responsible for the present state of affairs. McCollum, the dean of nutritionists, himself under such titles as "Common Sense and Nutrition" and "What is the Right Diet?" has continually stressed the importance of the right food rather than supplementary vitamins. He⁵⁹ brought out the fact that vitamin A is anti-infective merely in the sense that it prevents the typical keratinization of tissues produced by avitaminosis A and that it does not affect general immunity. He stated that from experiments there is no basis for the belief that vitamin A is clinically effective in infections caused by specific pathogenic organisms or in infectious disease unassociated with characteristic structural breakdown of epithelial tissue and the accompanying localized infection typical of vitamin A deficiency.

Wolbach early pointed out that the essential lesion in what has been made the classic example of vitamin deficiency and susceptibility to infection was not infection, but only keratinized epithelium which merely resembled pus, and infection was secondary.

Harris, Innes and Griffin⁴¹ emphasized that the existing data afforded no basis for the belief that vitamin A therapy is likely to be effective in combatting acute general infections due to specific pathogens or in infectious diseases or toxemias unassociated with the changes in epithelial tissue and localized infection characteristic of vitamin A deficiency.

Hess, Lewis and Barenberg⁴³ concluded that our dietary is not deficient in vitamin A, and a lack is present generally only as a result of such circumstances as poor selection of diet or defective absorption.

Studying the vitamin A reserve in over 300 specimens of human liver, Moore⁶⁵ found a wide variation in the amount present with adequate amounts in a wide variety of infective conditions. He qualified the term "anti-infection" as being justifiable only in a sense complementary to the idea that a deficiency of vitamin A leads to lowered resistance.

Although the mass of evidence is to the effect that susceptibility to a number of experimental infections can be influenced by drastic deprivation of vitamins, it is quite impossible to interpret the mass, or perhaps better, the maze of experimental evidence on vitamin deficiency and susceptibility to infection further than to point out that the premises which originally formed the basis of the idea are by no means sufficient to substantiate vitamin deficiency as an important principle in epidemiology.

In the first line of evidence, famine and pestilence, it is by no means clear that the nutritional deficiency itself makes for the occurrence of infectious disease through any lowering of resistance to infection. It would appear, rather, that pestilence following famine can usually be accounted for more properly as a secondary result of famine due to such factors as an accompanying breakdown in sanitation. This is not to say that disease, having developed, may not run a more severe course or be more highly fatal in nutritionally deficient people.

In the second of these lines, xerophthalmia, the idea of increased susceptibility to infection as such appears to be only in part correct. In the first place, aggregation of keratinized epithelial tissue, mistakenly called pus, appears to account for the emphasis on increased susceptibility; and in the second place, the infections which do occur in these cases are not

systemic epidemic infectious disease, but, rather, local tissue infections which find suitable soil in keratinized epithelium, and hence to be regarded as entirely secondary. Finally, this disease—the nearest approach we have to a nutritional deficiency as an epidemiologic determinant in infectious disease—is of extremely limited distribution, and in a pattern which can be accounted for on the basis of nutritional deficiency occurring in the same pattern. The distribution of disease always reflects its epidemiology. So far, in spite of numerous hypotheses which have been advanced so largely from “highly experimental findings,” one cannot point to a single epidemic disease which exhibits any distributional feature clearly or even partially corresponding to those of any known or even suspected nutritional deficiency. Nonetheless, from a few slender threads of fact, the supplementing of a dietary from the grocery store admittedly containing all the vitamins necessary to health (even though all may not, either by reason of incorrect selection, processing or cooking, or for economic reasons obtain a good dietary) by comparatively enormously more expensive drug store vitamins taken largely to ward off infections, has grown into one of the nation’s major commercial industries.

It has now reached the point, for example, where a falling off in the catch of soupfin sharks—an only recently added source of vitamin A—is viewed with alarm as an impending national calamity:

Perhaps the recent experimental demonstration—even more clear-cut than any of the experimental evidence to the contrary—that vitamin-deficient animals are actually *less* susceptible to a number of virus infections (and these account for the majority of our infectious disease) will serve to call a halt on what appears to be a needless and expensive and therefore inadequate way of insuring a “balanced diet” to our population.

This review prompts the formulation of the proposition that vitamin deficiency as a factor in susceptibility to infection is not a general epidemiologic principle. The indications are that only deficiencies of certain vitamins affect susceptibility to certain types of infections and that these occur only in limited areas where these vitamin deficiencies reach a sufficiently severe degree to produce tissue changes which are favorable sites for secondary infection.

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A CENTURY OF SUCCESSFUL PUBLICATION

The American Journal of the Medical Sciences desires to take this opportunity to congratulate the NEW ORLEANS MEDICAL AND SURGICAL JOURNAL, and DR. JOHN H. MUSSER, who has been its Editor for the last 17 years and was formerly editor of this journal, on the completion, last May, of its first 100 years of continuous publication. There are comparatively few medical journals that have survived such a long period of service. Among the existing journals in the English language, only four are able to point to such a record: The Edinburgh Medical and Surgical Journal (founded in 1805), the New England Journal of Medicine and Surgery (1812), The American Journal of the Medical Sciences (1820) and the Lancet (1825). The fact that the NEW ORLEANS MEDICAL AND SURGICAL JOURNAL has now entered this list of centenarians is evidence that, like its long-lived contemporaries, it has consistently maintained the highest possible standard of excellence and in so doing has been a powerful influence in the development of medical and scientific literature.

BOOK REVIEWS AND NOTICES

RORSCHACH'S TEST. 1. Basic Processes. By SAMUEL J. BECK, PH.D., Head of Psychology Laboratory, Department of Neuropsychiatry, Michael Reese Hospital, Chicago; Associate Professor of Psychology, Northwestern Univ. Foreword by WILLARD L. VALENTINE, PH.D., Head of Department of Psychology, Northwestern Univ. Pp. 223; 20 tables; 10 figs. New York: Grune & Stratton, 1944. Price, \$3.50.

RORSCHACH's ink-blot test cards provide a psychometric method whereby the subject's personality may be projected into a standardized environmental situation, thus offering a definite objective personality study. The author, who is less inclined to deviate from the teachings of the Master than are some others, has intended his book for the student and expert. Since he is not convinced that the group technique is of proven value, all responses were obtained from the individual; however, the use of group technique in the service will render its later evaluation possible. Rorschach's entire procedure includes scoring, tabulation of results and finally their interpretation. All of the subject's responses were written down *verbatim*, then "scored," *i. e.*, recorded in the accepted symbol language, but with no attempt at interpretation.

The author has employed some of the numerous Rorschach symbols, giving most space to the following: *Z*, the organization of activity, which in the main is concerned with the relations that one or more portions of the selection bear to each other; this part of the text is elucidated with 10 figures. *M*, the movement response, which represents the wish-fulfillment activities, similar to those in Freud's unconscious realm, and the dreamwork of other psychoanalysts. *FV* and *Y*, light determined response, response expressed by variations in light figure values. *F+* and *F-* include the form quality evaluation; the *+* sign indicating the response is a common one, while *-* means the response is a new one. This experienced psychologist and ardent Rorschach research worker, has provided a book that is very trustworthy, and that uses caution in those problems that are definitely controversial. N. Y.

BABY DOCTOR. By ISAAC A. ABT, M.D. Pp. 308. New York and London: Whittlesey House, McGraw-Hill, 1944. Price, \$2.50.

BABY DOCTOR may be described as a spirited anecdotal autobiography with an educational aim. It does more than portray the growth of a sagacious pediatrician-teacher from preliminary training to retirement age, though that tale is told richly with humor and good will. The book in addition is a résumé of the great progress attained by the new specialty of pediatrics during its first and fruitful half century. By the device of alternating amusing anecdotes with brief dissertations on medical problems, the author achieves an informatively charming personal history. I. W.

MANUAL OF UROLOGY. By R. M. Lecomte, M.D., F.A.C.S., Professor of Urology, Georgetown Univ. Medical Department; Member of the American Urological Association. Third ed. Pp. 305; 60 figs. Baltimore: Williams and Wilkins, 1944. Price, \$4.00.

THIS edition of a popular medical student's textbook continues to give "the beginner a groundwork of fundamentals on which to build a larger structure." A new section dealing with the innervation of the kidneys and pelvic viscera has been added. This includes several diagnoses and reviews the motor and

sensory pathways with particular reference to an interpretation of the mechanism of pain.

The discussion of the treatment of acute gonorrhea with sulfonamides is very brief, as is also the consideration of prophylaxis, so vital to our armed forces. On the whole, the subject matter is well proportioned and clearly presented. The light weight and dull finish of the paper is a boon to the reader.

H. S.

THE WAR AND MENTAL HEALTH IN ENGLAND. By JAMES M. MACKINTOSH, M.D., Professor of Preventive Medicine, Univ. of Glasgow. Pp. 91. New York: Commonwealth Fund, 1944. Price, \$.85.

DR. MACKINTOSH divides this thin volume of essays into 2 parts: the first group bearing the title "The Impact of War;" and the second, "Mobilization for Peace." The last 5 papers are of little general interest to the American reader since they deal for the most part with the difficulties which beset the various voluntary organizations which are concerned with mental health in Britain. The reader searches vainly for the connection with the "war" of Dr. Mackintosh's title. Even the section on rehabilitation does not mention the special and overwhelming problem of the mentally or physically disabled soldier. The first group of essays contains more valuable information.

Perhaps the best thing in the book is a letter which describes a rest center for bombed-out refugees. There is also a brief but excellent summary of the debit and credit of the government's evacuation of children. The author points out that careful planning is required to prevent maladjustment and heartbreak from marring the children's homecoming after the war. He impatiently dismisses the sentimental theory that "a thoroughly bad slum home in the city is better for a child than a good foster home in the country." Making smooth the return of children from a better to a worse environment will call for the concerted efforts of psychiatric social workers, child guidance clinics, and local health authorities.

D. P.

THE WOUNDED GET BACK. By ALBERT Q. MAISEL. Foreword by ROSS T. MCINTIRE, Rear Admiral, Medical Corps, U.S.N., The Surgeon General of the Navy. Pp. 230. New York: Harcourt, Brace, 1944. Price, \$2.50.

THE author, a correspondent granted special privileges by the Navy to inspect their hospital installations in the South Pacific, tells his story well. Though a layman, Maisel presents an account of military medical practice which will be of great interest to all physicians. Beginning with a description of the hospital ship Solace, the author discusses the base hospital in Auckland, the aerial evacuation of casualties by SCAT, the facilities at Guadalcanal and Tulagi, and includes an excellent discussion of the problem of malaria as met by our forces in these regions. Though dealing with a woeful subject, the author presents it in a manner so restrained, yet optimistic, that the book will be a source of comfort to all who have been left behind.

H. S.

PERSISTENCE AND CHANGE IN PERSONALITY PATTERNS. By KATHERINE ELLIOTT ROBERTS and VIRGINIA VAN DYNE FLEMING. Monographs of the Society for Research in Child Development, Vol. VIII, No. 3 (Serial No. 36). Pp. 206; 26 tables. Washington, D. C.: National Research Council, 1943. Price, \$1.50.

THIS Monograph reports a study of a group of women clients of the Advisory Service for College Women from the point of view of persistence and change in personality patterns. Traits such as self-confidence were traced through each client's life history to evaluate under what conditions they might persist or change. The studies are carefully made with the use of many psychological evaluations and specific tests.

Life history material is difficult to study under any method of scientific research and the authors have been reluctant to present their findings as conclusions. They have produced supporting data for theories which have been well accepted by psychiatrists and social workers, and they point out the need for more scientific research.

M. P.

ALLERGY IN PRACTICE. By SAMUEL M. FEINBERG, M.D., Associate Professor of Medicine and Chief of the Division of Allergy, Northwestern Univ. Medical School; President, American Association for The Study of Allergy, 1942-43. With the Collaboration of OREN C. DURHAM, Chief Botanist, Abbott Laboratories. Pp. 798; 36 figs. Chicago: Year Book Publ., 1944. Price, \$8.00.

The author presents a comprehensive and well-documented account of his subject. The first 4 chapters of the book deal with the general aspects of the problem of hypersensitivity in man. Then follows a detailed discussion of the different groups of allergens such as fungi, inhalants, foods, drugs and so forth. The 100 page chapter on pollens was written by Oren C. Durham. Numerous maps showing the distribution of many common plants as well as a brief consideration of the characteristic flora of each state should prove helpful to the physician.

The account of fungi as allergens is actually a short monograph on a subject in which the author has done much original work. He concludes "that airborne spores of common fungi constitute a major cause of allergic symptoms. The manifestations produced are mainly asthma and rhinitis." In view of the increasing interest in parasitic fungi, this indictment of the free living forms should be an added spur to the study of these plants, so long neglected by physicians.

Several chapters are devoted to the study of asthma and hay fever. The importance of contact dermatitis in wartime industry should have merited a more extensive discussion of this subject than it has received. Treatment is adequately dealt with. The author assumes that to treat the allergic patient it is first necessary to know something about the nature of allergy and the substances producing it. In supplying this information he succeeds very well.

H. S.

CLINICAL UROLOGY. By OSWALD SWINNEY LOWSLEY, A.B., M.D., F.A.C.S., Director of Department of Urology (James Buchanan Brady Foundation) of the New York Hospital; and THOMAS KIRWIN, M.A., M.S., M.D., F.A.C.S., Attending Surgeon of Department of Urology (James Buchanan Brady Foundation) of the New York Hospital. Drawings by WILLIAM P. DIDUSEH. Second ed. Vols. 1 and 2. Pp. 1789; 220 figs.; 365 illus. Baltimore: Williams & Wilkins, 1944. Price, \$10 set of 2 Vols.

The first edition of this work, presented in 1940, was enthusiastically received as an authoritative and easily read treatise on urology. The many rapid advances in the urologic field have made necessary the presentation of a new edition. The stated purpose of the authors is to present "a practical survey of the nature, diagnosis, and treatment of anomalies and diseases of the genitourinary organs." According to the present stage of knowledge this purpose is accomplished. The volumes contain not only information on the urologic problems of the adult male, but also the problems concerning urology in women and children. It is written for the use of medical students, general practitioners, general surgeons, and urologists.

The first 5 chapters concern general diagnostic procedures; Chapter VI is on anesthesia; subsequent chapters take up the urogenital organs in anatomic sequence from without inward. For each organ there is a consideration of the embryology, anatomy, anomalies, physiology, injuries and diseases. Surgical and non-surgical therapy are discussed. The authors' methods of therapy

are emphasized, but they draw freely from the literature the opinions of other authorities.

New subjects presented in this edition are: the renal factor in hypertension, surgical treatment of arterial hypertension, calyceal resection, castration and hormonal treatment of carcinoma of the prostate, tidal drainage, continuous spinal anesthesia, dried blood plasma, new diets as related to urinary calculus, and methods of dissolving certain urinary calculi. New advances in chemotherapy as applied to gonorrhea, non-specific urinary infections, and pre- and postoperative treatment are thoroughly covered.

There is an extensive bibliography following each chapter. These comprehensive lists of references should be of great value to anyone desiring to go more deeply into any specialized subject.

From every angle this treatise is a most worth-while contribution to the urologic literature.

L. La T.

THE ELECTROCARDIOGRAM. ITS INTERPRETATION AND CLINICAL APPLICATION.

By LOUIS H. SIGLER, M.D., F.A.C.P., Attending Cardiologist and Chief of Cardiac Clinics, Coney Island and Harbor Hospitals; Formerly Instructor in Medicine, N. Y. Post Graduate Medical School, Columbia University. Pp. 403; 203 illus. and plates. New York: Grune & Stratton, 1944. Price, \$7.50.

THIS book is definitely more than "just one more book on ECG." The spate of such publications has subsided in recent years, so that presentations of recent developments, such as the criteria for right versus left ventricular premature contractions, right versus left bundle branch block, signs of myocardial disease, chest leads, and the effects of coronary occlusion, etc., are conveniently found well considered in this up-to-date presentation. The underlying principles are covered briefly in the first 4 chapters. Here one regrets that more attention was not given to the ventricular layers with their autonomous vascular and conductive tissue connections. One misses, also, consideration of Wolferth's views (1942) on the distribution of potential, which are at variance with the electrical axis concept. In the clinical sections, a historical note, incidence, pathologic anatomy (miscalled "pathology"), and physiologic mechanisms are included for each condition, whenever pertinent. Full references are given at the end of each chapter, and the illustrations are numerous and adequate though they lack the uniformly technical excellence that we often find in books of this class; and the price is high.

The Author appears to have made good use of his acquaintance with ECG literature, and of a considerable personal experience, in this presentation. The possibilities and limitations of the method in the various diseased conditions of the myocardium, as well as in the arrhythmias, have obviously been carefully considered.

E. K.

DER SCHWUND TUBERKULÖSER LUNGENKAVERNEN. By PROF. WALTER BERBLINGER, M.D. Pp. 130; 61 illus. Basel: Benno Schwabe, 1943. Price, 15 Swiss Fr.

THIS monograph deals with the processes involved in the healing and eradication of pulmonary tuberculous cavities. Berblinger reviews at considerable length the views of various pathologists relative to the possibility and mechanism of cavity eradication. It is noteworthy that Aschoff held that healing of tuberculous cavities was impossible without surgical intervention. The author reviews his experience with 32 cavities which had been under the suction treatment of Monaldi for periods up to 20 months. When their lungs were studied after the death of the patient, he could not establish a single case of cavity eradication. Prolonged drainage cleanses the cavity of its caseous contents, shrinks its walls, but never completely eradicates the specific tuberculous inflammatory changes in its walls. Though the sputum of such cases may become free of tubercle bacilli there is no certainty that,

with a change for the worse of the immunologic state of the patient, exacerbation may not take place. Only small elastic cavities can heal in such manner. Larger cavities, whether of the elastic or rigid wall type, can heal only by the occlusion of the exit bronchus or bronchi of the cavity which initiates the conversion of the cavity into a closed lesion. The author presents a detailed study of 9 cavities which had been observed by Roentgen ray during the life of the patients and were subsequently thoroughly investigated on the death of the individual. He comes to the conclusion that the factor of paramount importance in the healing of cavities is the permanent closing of the bronchi into which these cavities lead. He presents convincing evidence that the process begins as a tuberculous bronchitis which often originates at a considerable distance from the cavity. A non-specific inflammatory process then closes the bronchus beyond the tuberculous bronchitis and nearest the cavity. Once these bronchi are thoroughly closed, the bacilli in the cavity are deprived of oxygen and die off. The contents of the cavity become thickened by absorption of their moisture. The progression of the tuberculous process in the wall ceases and the inspissated contents are gradually absorbed by the surrounding tuberculous granulation tissue. He emphasizes that the outgoing bronchus is sealed before the cavity heals, for which he presents clear pathologic evidence. After the absorption of the caseous tissue from the center of the cavity the space is replaced by dense fibrous tissue. Often the wall of the exit bronchi becomes enmeshed in this scar which then has a characteristic appearance as given by the islands of cartilage that are seen in these scars.

This is a thorough, comprehensive though somewhat repetitious paper, and is of great value to all students of tuberculosis.

M. L.

ONE HUNDRED YEARS OF AMERICAN PSYCHIATRY. Published for *The American Psychiatric Association*. By the following Contributors: HENRY ALDEN BUNKER, ALBERT DEUTSCH, J. K. HALL, SAMUEL W. HAMILTON, CLYDE KLUCKHOHN, WILLIAM MALAMUD, DOM THOMAS VERNER MOORE, WINFRED OVERHOLSER, RICHARD H. SHRYOCK, HENRY E. SIGERIST, EDWARD A. STRECKER, JOHN C. WHITEHORN, GREGORY ZILBOORG. Foreword by GREGORY ZILBOORG. Introduction by J. K. HALL. Pp. 649; 35 illus. New York: Columbia Univ. Press, 1944. Price, \$6.00.

AMERICAN Psychiatry has indeed progressed far since the foundation of the American Psychiatric Association just 100 years ago, when lunatics were "put away" in an "insane asylum" for the protection of society and the convenience of relatives; and further still has it progressed since 100 years before that when lunatics were treated with whips and chains, as at the Pennsylvania Hospital (founded in 1751, the first in this country) to take philanthropic care of the sick and wounded. Yet, as Shryock here points out in the chapter on the Beginnings, brutality at that time was the rule—even the "relatively humane" Benjamin Rush advocated the "tranquilizer" and a whirling "gyrator" long after the gentle John Howard had done his work in England, and Pinel had struck off the chains from the insane at the Bicetre (1792).

In the handsome volume now before us, one gets a full view of 100 years of psychiatry in this country, from the descriptions of the mental hospitals, of psychiatric research and literature, psychiatric therapies, and especially of the American Psychiatric Association—which, known at first as the Association of Medical Superintendents of American Institutions for the Insane, celebrated its centenary at Philadelphia, its birthplace, last May. An authoritative, well documented production, the work is necessarily of interest chiefly to psychiatrists; however, Shryock's and Sigerist's opening chapters should have a much wider appeal, as should also such items as the fact that the American Psychiatric Association was the only national medical body in existence in this country 100 years ago, and that the American Journal of Insanity, just

3 months older than the Association, was the first periodical in English to be devoted to mental disease.

Psychiatry has become increasingly recognized by both medico and layman as one of the most important branches of medicine, to which fact this book amply testifies. The portrayal of the evolution of American psychiatry and its present trends and accomplishments is given in such detail that it is beyond the power of the Reviewer, not a psychiatrist himself, to evaluate. It should not seem altogether captious, however, to call attention to a frequently repeated criticism of psychiatry, namely, that in these days of medical objectivity, which gained momentum just about the time the American Psychiatric Association was being founded, psychiatry has lagged behind other medical disciplines in cultivating this quality. The nature of the human mind and its malfunctioning is, of course, chiefly responsible; but it is only since the last war that this lack of objectivity has been appreciated (Cp. Freud's lack of even statistical control of his psychoanalytic assertions). One wonders whether even today the average psychiatrist is sufficiently concerned about this shortcoming. Indeed, may not this be an important basis for the frequent criticism that in psychiatric studies "everyone has to start from scratch all over again." In the evaluation of psychiatric therapies, the empirical method still rules supreme; even in the recently introduced shock therapies we hear much about the comparative results of this or that form of shock or the best dosage in this or that condition, but painfully little that is objective as to why they are of use, or about the anatomical changes they produce. Such an uncertain basis may be of some use, but it is not the way that the nosology of internal diseases was established, that tuberculosis and other communicable diseases were conquered, or the efficiency of the sulphonamides and of penicillin proved. Could it be that another Weir Mitchell, as in 1894, is needed to jolt more of psychiatric research into objective lines? To be sure, Whitehorn's chapter on Psychiatric Research indicates that in certain centers there has been considerable research in recent years; yet the story of all phases of psychiatric research occupies but 27 of more than 600 pages of this book, and there is only one reference to work published before 1894 and only a dozen before the first World War.

The book is well presented and inexpensive for one of its size and quality. The illustrations also are good, though not too numerous and annoyingly separated from the text that they illustrate. The answer to possible criticism of the handsome format and quality of the paper used is, we understand, that pertinent preparations for the volume's publication had already been accomplished before the war time restrictions on printing paper, etc., had been put into effect. The obvious care and thought that have been put into this Centenary Volume have borne good fruit and a valuable chapter has been written into the history of American medicine.

E. K.

PSYCHIATRY AND THE WAR. A Survey of the Significance of Psychiatry and Its Relation to Disturbances in Human Behavior to Help Provide for the Present War Effort and for Post War Needs. Edited by FRANK J. SLADEN, M.D., Physician-in-Chief, Henry Ford Hospital, Detroit Trustee, McGregor Fund. Contributions of the Conference on Psychiatry of the Univ. of Michigan and McGregor Fund. Pp. 505. Springfield, Ill.: Charles C Thomas, 1943. Price, \$5.00.

In this volume are gathered together some 30 papers and 2 symposia originally presented at the Ann Arbor Conference on Psychiatry held in October, 1942. Most of the best known names in American psychiatry may be found among the list of authors. Part 1 deals with the "Philosophy of Psychiatry," and comprises articles on the significance of psychiatry in sister disciplines such as pediatrics, geriatrics and internal medicine. Dr. Percival Bailey has contributed a particularly incisive paper on psychiatry and general surgery. Part 2 covers the topic "Research in Psychiatry." Part 3 is entitled "Psychiatry in the Training, Experience and Education of the Individual." Only

in Part 4, "Psychiatry and the War," do we find papers dealing with the psychiatric implications of the present world cataclysm.

One questions the propriety of the title given to a volume which devotes two-thirds of its text to matters not connected with war. One also questions the value of the book as a whole. Are short, 20-minute papers able to do justice to topics such as "Psychiatry and Family Life," "Psychiatry and Religion," "Psychiatry, Its Meaning and Scope"? This book is a collection of little papers on big subjects. Inevitably, the writers are somewhat overwhelmed by the topics selected for them.

D. P.

MEDICAL EDUCATION IN THE UNITED STATES BEFORE THE CIVIL WAR. By WILLIAM FREDERICK NORWOOD, Associate Professor of the History of Medicine and Associate Dean in the School of Medicine, College of Evangelists, Los Angeles. Foreword by HENRY E. SIGERIST, Pp. 464. Philadelphia: Univ. of Penna. Press, 1944. Price, \$6.00.

THIS carefully prepared, well documented, detailed, and unbiased study of American Medical Education during most of its preparatory period amply fulfills the Author's self imposed task of surveying "the rise and progress of the American system of medical instruction and the institutions of medical learning up to the time of the Civil War." Dr. Norwood's reasons for stopping at this point (closure of the Southern medical schools, the end of the critical period in the medical reform movement of the fifties, the Civil War's temporary stalemating of the movement to elevate medical education, and the bulkiness necessitated by inclusion of a longer period) are good and sufficient. Except for the lack of a sharp chronological end-point, however, it might more logically have been carried to the beginning of the renaissance in American Medical Education in the 70's; but this is by no means a vital consideration. Let us hope that a later volume—to which, for a while in these transition days, every succeeding year will be adding important material—will be forthcoming before too much time has elapsed and too much water has gone over the dam!

E. K.

TECHNIQUE IN TRAUMA. Planned Timing in the Treatment of Wounds Including Burns. From The Montreal General Hospital and McGill Univ. By FRASER B. GURD, M.D., C.M., and F. DOUGLAS ACKMAN, M.D., C.M. In collaboration with JOHN W. GERRIE, M.D., C.M., EDWARD S. MILLS, M.D., C.M., JOSEPH E. PRITCHARD, M.D., FREDERICK SMITH, M.D. Preface by JOHN S. LOCKWOOD, M.D., Univ. of Penna., and Commentary by RALPH R. FITZGERALD, M.D., C.M., McGill Univ. Pp. 68; 17 figs.; 5 tables; 3 charts; 3 color charts; 3 color plates. Philadelphia: J. B. Lippincott, 1944. Price, \$2.00.

THIS monograph contains 3 excellent articles reprinted from the *Annals of Surgery*, with additional text, with a commentary by Ralph R. Fitzgerald. The authors' practice and case reports are well set forth and are extremely interesting and valuable. Along with most other authors they have given up coagulation treatment of burns, and have laid down their step-by-step rules for the care of burns and wounds.

The work is a convenient form for reading, and if more widely adopted would help settle the "reprint problem" for both author and reader.

J. B.

SYNOPSIS OF MATERIA MEDICA, TOXICOLOGY, AND PHARMACOLOGY. For Students and Practitioners of Medicine. By FORREST RAMON DAVISON, B.A., M.Sc., Ph.D., M.B., Formerly Assistant Professor of Pharmacology in the School of Medicine, Univ. of Arkansas, Little Rock; Medical Department, The Upjohn Co., Kalamazoo, Mich. Third ed. Pp. 759; 40 illus. (4 in color); 35 tables. St. Louis: C. V. Mosby, 1944. Price, \$6.50.

NEW editions of pharmacology texts can be evaluated best by comparison with the standard book in this field, Goodman and Gilman's "Pharmacological

Basis of Therapeutics;" such a comparison is decidedly unfavorable to Davison's 3rd edition. The latter suffers by the advocacy of many unsound procedures (such as the use of low chloride diet to eliminate bromide, the use of morphine in asthma, arsenic in malaria, atropine to arrest gastric and pancreatic secretions, 10% CO₂ inhalations for 5 to 10 minutes, etc.). In addition Davison often shows a poor understanding of physiologic mechanisms (see section on autonomic nervous system, renal function, anoxia). The diagrams are long outdated and often poorly chosen, the arrangement is not ideal ("miscellaneous drugs" include antimalarials, parenteral solutions, therapeutic gases, and sodium thiosulfate), the apothecaries system is often given preference over the metric, and there are numerous contradictions to confuse the student. This synopsis illustrates again the frequent association of inaccuracy with attempted condensation of a major medical science; nevertheless Davison's remains the best of the shorter books on Pharmacology.

J. C., JR.

THE 1943 YEAR BOOK OF PEDIATRICS. Edited by ISAAC A. ABT., D.Sc., M.D., Professor of Pediatrics, Northwestern Univ. Medical School; Attending Physician, Passavant Hospital; Consulting Physician, Children's Memorial Hospital and St. Luke's Hospital, Chicago. With the Collaboration of ARTHUR F. ABT, B.S., M.D., Associate Professor of Pediatrics, Northwestern Univ. Medical School; Associate Attending Pediatrician, Michael Reese Hospital; Attending Pediatrician, Chicago Maternity Center; Attending Physician, Spaulding School for Crippled Children and La Rabida Jackson Park Sanatorium, Chicago. Pp. 448; 76 figs. Chicago: Year Book Publishers, 1944. Price, \$3.00.

THE Year Book of Pediatrics is a collection of half-page or 2-page abstracts of the more important yearly contributions to pediatric literature. The several hundred articles reviewed have been selected with discrimination, and prepared with intelligent care. The abstractors have succeeded in conveying to the reader the meaty chief points of the original authors' presentations. Occasional notes inserted by the editor, and a large number of reproduced illustrations, add to the interest and value of the text. For the specialist this book is of value as a time-saving survey of annual progress; the general practitioner will find in it handy summaries of the latest views on nutrition, prophylaxis, diagnosis and treatment. The broad sweep of territory comprehended within the indefinite limits of pediatrics is emphasized by the fact that in a compilation such as this, only a small percentage of the articles quoted are from the familiar pediatric journals. The great majority have had to be picked from the great body of medical periodicals, native and foreign, which the average doctor never sees unless in the habit of browsing conscientiously through the reading room of a fine medical library.

I. W.

INTRACRANIAL ARTERIAL ANEURYSMS. By WALTER E. DANDY, Adjunct Professor of Surgery in The Johns Hopkins Univ. Pp. 147; 55 figs.; 5 tables. Ithaca, N. Y.: Comstock Pub. Co., Cornell Univ., 1944. Price, \$2.50.

DR. DANDY presents in his latest monograph the results of probably the widest experience in the surgical attack of these formidable lesions. The general symptomatology, including the occasional occurrence of epilepsy and migraine, is discussed in detail. Consideration of the symptom-complexes caused by aneurysms arising from the various portions of the internal carotid artery and the Circle of Willis fails to establish clear localizing syndromes. Angiography was not generally employed and the consideration given this subject is meager. The potential value of the method is freely admitted, but Dr. Dandy has been fearful of the production of cerebral thrombi. It would seem that the wide experience of the many who have used thorotrast as the contrast media, without undue complications, would offset this fear.

A well-presented chapter on the embryology, anatomy and variations of

the Circle of Willis by D. H. Padget is included in this monograph. The relationship of the developmental anatomy of the Circle of Willis and the sites of the aneurysms found leads the authors to offer the well-conceived hypothesis that a congenital aneurysm occurs in connection with the incomplete involution of a temporary embryonic branch.

The surgical principles are clearly presented; the experiences detailed, some of them hair-raising, should be of immense help to those who would treat these lesions. Unfortunately, some confusion is caused by the failure to identify the cases considered in the text by other than their number in the series. This causes much turning back and forth from the unwieldily attached master tables in the back of the book for the reader to be fully oriented.

The illustrations, as is usual in Dr. Dandy's monographs, are excellent. The above-mentioned master tables, though difficult to handle, are of great value for detailed consideration of the case material. This monograph should serve well Dr. Dandy's purpose; that of stimulating the attack against these heretofore hopeless situations.

H. S.

ANATOMY AND PHYSIOLOGY. Laboratory Manual. By CATHERINE PARKER ANTHONY, B.A., R.N., Instructor of Anatomy and Physiology, Lutheran Hospital, Cleveland, Ohio; Formerly Instructor of Anatomy and Physiology, St. Luke's Hospital, Cleveland, Ohio, and Assistant Instructor of Anatomy and Physiology, Frances Payne Bolton School of Nursing, Western Reserve Univ. Pp. 249; many illus. St. Louis: C. V. Mosby, 1944. Price, \$2.00.

THIS manual offers basic material for a laboratory course in anatomy and physiology to preclinical nursing students, as a means of amplifying the textbook and lecture material.

The manual can be used for 30 to 70 laboratory hours. It follows closely the unit plan suggested in the Curriculum Guide for Schools of Nursing. Especially useful to instructors are suggestions for teaching hours and a list of equipment and material for each laboratory period.

This book may be used profitably in a school in which mimeographed laboratory sheets are not easily available and in which the laboratory work is not based on human or mammalian dissection by students. It may be correlated successfully with any standard textbook of anatomy and physiology for nurses.

H. F.

BACTERIAL INFECTION with Special Reference to Dental Practice. By J. L. T. APPLETON, B.S., D.D.S., Sc.D., Professor of Bacteriopathology and Dean, The Thomas W. Evans Museum and Dental Institute, School of Dentistry, Univ. of Pennsylvania. Third ed., thoroughly revised. Pp. 498; 86 engravings; 5 plates. Philadelphia: Lea & Febiger, 1944. Price, \$7.00.

THE author presents a thoroughly revised text on the host-parasite relationship with special reference to dental practice. The book was written for two purposes: (1) to give a comprehensive concept of infectious disease, and (2) to point out wherever a knowledge of infection will help the dentist in understanding or in solving his problems.

To carry out these purposes the book has been divided into 3 parts: Part I giving a minimum background on the morphology, physiology and ecology of the bacteria and filterable viruses; Part II treating the subject of infection in general; and Part III discussing the infections associated with the oral cavity and stressing the importance of dental health and infection in the general health of the patient.

In this 3rd edition, there has been increased emphasis placed on asepsis and surgical antisepsis. Part I has been increased to include material on the Pure Culture Study of Bacteria. Chapters have been added on the Ecology of Microorganisms of the Mouth, Actinomycosis and Osteomyelitis. The author stresses the importance of Oral Hygiene and places it as the ultimate goal of the text.

This text should have great value in the teaching of dentistry and in dental practice. First, to give the student the theories and fundamentals of infection and resistance to infection, and second, to give the practising dentist the practical points in understanding and solving his problems of asepsis and antisepsis as well as the rôle of the dental health in the general health of the patient.

F. E.

PHYSICAL FOUNDATIONS OF RADIOLOGY. By OTTO GLASSER, PH.D., Professor of Biophysics and Head of Department of Biophysics, Cleveland Clinic Foundation, Cleveland, Ohio; EDITH H. QUIMBY, Sc.D., Associate Professor of Radiology (Physics), College of Physicians and Surgeons, Columbia Univ., New York; LAURISTON S. TAYLOR, PH.D., Chief of X-ray Section, National Bureau of Standards, Washington, D. C.; and J. L. WEATHERWAX, M.A., Philadelphia General Hospital and Graduate School of Medicine, Univ. of Pennsylvania, Philadelphia. Pp. 426; 95 figs.; 43 tables. New York and London: Paul B. Hoeber, 1944. Price, \$5.00.

THE editorial team of this book leaves nothing to be desired. The editors are four authoritative physicists who have worked in the field of therapeutic radiology for many years. They have taught many students and know the weaknesses of physical education that is manifest in young doctors seeking training in radiology. In a small monograph of 426 pages, these authors have considered in a masterly way the various aspects of the physical problems of corpuscular and the electromagnetic wave radiation, the fundamentals of electricity and magnetism, high voltage generators and Roentgen ray tubes, radioactivity—natural and artificial—the physical principles of Roentgen ray diagnostic features, the measurements of Roentgen ray and radium protection, and biologic reactions to radiation.

This book is prepared in such a way that it is easily understandable to one who has had a moderate amount of training in college physics. It supplies a real need in therapeutic and diagnostic physics.

Most of these authors have contributed many articles to the subjects discussed in this book, and it is from that background that they have provided an excellent small monograph. They have included an adequate number of diagrams and tables to explain most of the simple problems that confront the radiologist.

The publisher has provided good paper and most satisfactory printing. The Reviewer regards this book as an essential part of every radiologist's library.

E. P.

CÆSAREAN SECTION. The History and Development of the Operation From Earliest Times. By J. H. YOUNG, M.B., Ch.B., D.T.M. and H. (Edin.). Foreword by MILES H. PHILLIPS, M.D. (Hon.), B.S., F.R.C.S., F.K.C.O.G. Pp. 254; 22 tables. London: H. K. Lewis, 1944. Price, 16s.

ANY exhaustive contribution to the history of medicine is very welcome, and especially one that deals with a procedure employed so universally as the delivery of the infant by the abdominal route. Young has made just such a contribution in his volume dealing with cæsarean (or as we Americans are accustomed to spell the word, cesarean) section. This book not only supplies a remarkably full history of this classical operation but also stresses the development of the various modifications of the operation. Many interesting cases are cited, including mention of the first operation performed in the United States (1822). The patient, a 14 year old quadroon, illegitimately pregnant with twins, opened her own abdomen with a razor while lying on a snowbank. Her first infant was born *per vias naturales*, and its twin through the abdominal wall. The patient survived her operation, and was known to be living 6 years later.

The volume is fully documented and contains a complete bibliographic index. Although the extraperitoneal operation is considered, the omission of the Waters technic, developed in this country, no doubt resulted from the

fact that it is a very recent development. The Reviewer recommends this important volume to all obstetricians, and to every one interested in the history of surgery.

D. M.

HYDRONEPHROSIS AND PYELITIS (Polynephritis) OF PREGNANCY. Etiology and Pathogenesis. An Historical Review. By H. E. ROBERTSON, M.D. Philadelphia: W. B. Saunders, 1944. Price, \$4.50.

Too often the practitioner of medicine is conversant only with the dominant contemporary theories of disease, and is wholly ignorant of their origins. This scholarly review of the development of our concepts of hydronephrosis and pyelitis in pregnancy is proof that American medicine has reached the stage where it may pause now and then to evaluate contemporary opinion in the light of previous experience. How thoroughly the author has done this for his chosen subject is indicated by the length of the bibliography which numbers almost 1000 entries. Unique is a chapter devoted to a review of textbooks and their method of dealing with the problem. For the textbook, even more than the original article, moulds the pattern of thought in each new generation of physicians. It is hoped that this monograph will be only the first of many dealing with the "Entwicklungsmechanik" of modern medicine.

H. S.

AUTONOMIC REGULATIONS. By ERNST GELLHORN, M.D., PH.D., Professor of Physiology, College of Medicine, Univ. of Illinois. Pp. 373; 80 illus. New York: Interscience Publishers, Inc., 1943.

This book is a compounding of some 55 original papers published by the author during the years 1939-1942, along with a review of the literature. Some of the material represents unpublished observations of the author, much of it unconfirmed and not infrequently comprising evidence apparently obtained from a single animal experiment. The book is highly repetitious, and one has the feeling that the subject matter might have been presented better, with less confusion, in considerably less space. Nevertheless, it contains interesting data which should be unusually stimulating to investigators.

J. C.

MANUAL OF HUMAN PROTOZOA. By RICHARD R. KUDO, D.Sc., Associate Professor of Zoölogy, The University of Illinois. Pp. 125; 29 figs. Springfield, Ill.: Charles C Thomas, 1944. Price, \$2.00.

This little book contains all the information necessary for efficient examination of blood, tissues and excretions to determine whether or not protozoan parasites are present. Descriptions are complete, drawings accurate—although they do not allow for variations—and directions are clearly worded. It will be especially valuable to technicians in clinical laboratories.

H. R.

MANUAL OF THE DISEASES OF THE EYE. By CHARLES H. MAY, M.D., Consulting Ophthalmologist to Bellevue, Mt. Sinai and French Hospitals, New York; Formerly Chief of Clinic and Instructor in Ophthalmology, Medical Department of Columbia Univ.; and Director of the Eye Service at Bellevue Hospital, New York. With the assistance of CHARLES A. PERERA, M.D., Associate in Ophthalmology, College of Physicians and Surgeons, Medical Department of Columbia Univ., New York; Assistant Attending Ophthalmologist, Presbyterian Hospital, New York. Eighteenth ed. Pp. 520; 387 figs. (32 plates, 93 colored figs.). Baltimore: William Wood., 1943. Price, \$4.00.

This new edition retains the excellence of previous ones as a textbook for students and general practitioners. There are many minor changes and corrections. The sections on therapy of the various ocular infections now include

the use of penicillin, as well as the more recent sulfa drugs. The sections on compensation for eye injuries and the ocular requirements for admission to the various armed services have been brought up to date. F. A.

PRACTICAL MALARIAL CONTROL: A HANDBOOK FOR FIELD WORKERS. By CARL E. M. GUNTHER, M.D., B.S., D.T.M. (SIDNEY), Field Medical Officer, Bulolo Gold Dredging Limited, Territory of New Guinea, at present with the Australian Medical Corps. Foreword by PROF. HARVEY SUTTON, O.B.E., M.D., F.R.A.C.P., B.Sc., D.P.H., F.R.SAN.I. Pp. 91. New York: Philosophical Library, 1944. Price, \$2.50.

THIS practical handbook is concerned with the problem of control, diagnosis and treatment of malaria. The experience of the author is extensive and it should prove to be a valuable guide to those combating malaria in the field. However, his recommendations on the drug prophylaxis and treatment of malaria do not agree with the current concepts originating from the Offices of the U.S.A. Surgeons-General. The use of thick films in the diagnosis of malaria should be more fully dealt with, as it is now a recognized practical field method. The discussion of mosquito control methods is excellent and would alone be sufficient to recommend the book. R. J.

NEW BOOKS

Urological Surgery. By AUSTIN INGRAM DODSON, M.D., F.A.C.S., Professor of Urology, Medical College of Virginia; Urologist to the Hospital Division, Medical College of Virginia; Urologist to Crippled Children's Hospital; Urologist to St. Elizabeth's Hospital; Urologist to St. Luke's Hospital and McGuire Clinic. With contributions by 7 well-known authorities. Pp. 768; 576 illus. St. Louis, C. V. Mosby, 1944. Price, \$10.00.

Fertility in Women. By SAMUEL L. SIEGLER, M.D., F.A.C.S., Attending Obstetrician and Gynecologist, Brooklyn Women's Hospital; Attending Gynecologist, Unity Hospital; Assistant Obstetrician and Gynecologist, Greenpoint Hospital; Attending Sterility Clinic, Greenpoint Hospital; Consultant in Gynecology, Rockaway Beach Hospital; Diplomate, American Board of Obstetrics and Gynecology; Fellow, New York Academy of Medicine; Member, Society for the Study of Internal Secretions. Foreword by ROBERT LATOU DICKINSON, M.D. Pp. 450; 194 illus. Philadelphia, J. B. Lippincott, 1944. Companion book to *Fertility in Men*. In slip case, \$8.00.

Fertility in Men. By ROBERT SHERMAN HOTCHKISS, B.S., M.D., Lt. COMM. (M.C.), U.S.N.R. (on active service), Assistant Professor of Urology, New York Univ. Medical College; Instructor in Surgery (Urology), Cornell Medical College; Assistant Visiting Attending Physician, Department of Urology, Bellevue Hospital; Assistant Visiting Attending Physician in Surgery (Urology), New York Hospital; Chief of Urological Clinic, New York Univ. Medical College Clinic. Foreword by NICHOLSON J. EASTMAN, M.D. Pp. 216; 95 illus. Philadelphia: J. B. Lippincott, 1944. Companion book to *Fertility in Women*. In slip case, \$8.00.

Hypertension and Hypertensive Disease. By WILLIAM GOLDRING, M.D., and HERBERT CHASIS, M.D. Dedication to HOMER W. SMITH. Pp. 253; 53 figs. New York: The Commonwealth Fund, 1944. Price, \$3.50.

Rebel Without a Cause. The Hypoanalysis of a Criminal Psychopath. By ROBERT M. LINDNER, PH.D., U. S. Public Health Service (R), Psychologist; U. S. Penitentiary, Lewisburg, Pa.; Lecturer in Criminology, Bucknell Univ. Introduction by SHELDON GLUECK, LL.B., PH.D., and ELEANOR T. GLUECK, Ed.D. Pp. 295. New York: Grune & Stratton, 1944. Price, \$4.00.

Technic of Electrotherapy and Its Physical and Physiological Basis. By STAFFORD L. OSBORNE, M.S., PH.D., Assistant Professor, Department of Physical Therapy, Northwestern Univ. Medical School; and HAROLD J. HOLMQUEST, B.S., B.S.(M.E.), Lecturer in Applied Physics, Dept. of Physical Therapy, Northwestern Univ. Medical School. Pp. 780; 240 figs., having 293 illus.; 72 tables. Springfield, Ill.: Charles C Thomas, 1944. Price, \$7.50.

Medical Education in the United States Before the Civil War. By WILLIAM FREDERICK NORWOOD, Associate Professor of the History of Medicine and Associate Dean in the School of Medicine, College of Evangelists, Los Angeles. Foreword by HENRY E. SIGERIST. Pp. 464. Philadelphia: Univ. of Pennsylvania Press, 1944. Price, \$6.00.

Organic Chemistry. By LOUIS F. FIESER, Sheldon Emery Professor of Organic Chemistry, Harvard Univ.; and MARY FIESER, Research Chemist. Pp. 1112; numerous illustrations. Boston, Mass.: D. C. Heath, 1944. Price, Trade Edition, \$8.00; College Edition, \$6.00.

The Romance of Medicine. The Story of the Evolution of Medicine From Occult Practices and Primitive Times. By BENJAMIN LEE GORDON, M.D., Member, American Association of the History of Medicine; Attending Ophthalmologist to the Shore Memorial Hospital, Somers Point, N. J., and to Atlantic County Hospital for Tuberculosis, Northfield, N. J. Authorized Medical Examiner for Civil Aeronautics Administration, Dept. of Commerce, Washington, D. C. Formerly Associate Ophthalmic Surgeon of St. Agnes Hospital, Philadelphia. Pp. 624; 147 illus. Philadelphia: F. A. Davis, 1944. Price, \$5.00.

NEW EDITIONS

The Youngest of the Family. A Manual for the Inexperienced Mother. By JOSEPH GARLAND, M.D., Physician to Children's Medical Dept., Massachusetts General Hospital; Consulting Pediatrician, Massachusetts Eye and Ear Infirmary; Instructor in Pediatrics, Harvard Medical School. Revised ed. Pp. 182. Cambridge, Mass.: Harvard Univ. Press, 1943. Price, \$2.00.

Quick Reference Book for Medicine and Surgery. A Clinical, Diagnostic, and Therapeutic Digest of General Medicine, Surgery, and the Specialties. By GEORGE E. REHBERGER, A.B., M.D. Twelfth ed. Pp. 1460. Philadelphia, London, Montreal: J. B. Lippincott, 1944. Price, \$15.00.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMHAAER, School of Medicine, University of Pennsylvania, Philadelphia 4, Pa. Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

MANUSCRIPTS should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. ILLUSTRATIONS accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. The recommendations of the American Medical Association Style Book should be followed. REFERENCES should be numbered and at the end of the articles, arranged alphabetically according to the name of the first author and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers).

RETURN POSTAGE should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

For the balance of the war, 150 REPRINTS will be supplied gratis. Covers will be omitted on all articles. In ordering additional reprints, we will supply in multiples of 150.

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

OCTOBER, 1944

ORIGINAL ARTICLES

ON THE DIAGNOSIS OF HEMORRHAGE IN MAN

A STUDY OF VOLUNTEERS BLED LARGE AMOUNTS

BY H. A. SHENKIN, M.D., R. H. CHENEY, M.D., S. R. GOVONS, M.D.,
J. D. HARDY, M.D., A. G. FLETCHER, JR., M.D.

AND

ISAAC STARR, M.D.

PHILADELPHIA, PA.

(From the Research Department of Therapeutics, the Neurosurgical Service and the Medical Division of the Hospital of the University of Pennsylvania)

THAT hemorrhage can be diagnosed by a rapid pulse and a low blood pressure is a concept so widely accepted that it seems almost an impertinence to question it. We were first led to do so by observations made on patients after operation on the neurosurgical service. White's observations¹⁶ had disclosed that the loss of blood in major neurosurgical operations was much larger than had been suspected, and his estimates of the amount lost, from 1 to 2 liters, were confirmed in this hospital by Webster.¹⁴ However, after operations in which much blood was undoubtedly lost, some patients showed none of the signs ordinarily expected after so large a hemorrhage.

Further reflection on this situation forced us to admit that exact knowledge of the symptoms following hemorrhage in man was scanty and to wonder by what means this condition could be diagnosed in patients not seen until after hemorrhage had taken place. This matter seemed of especial importance in war time; and it was, therefore, decided to bleed volunteers and study the manifestations which followed in order to improve our ability to detect the abnormalities following hemorrhage. Furthermore, such a project would throw light on the important question of how much blood donors should be asked to give with due regard to their safety.

While therapeutic bleeding is no longer commonplace, the removal of 400 to 500 cc. from blood donors has become so. The effect of bleeding in amounts larger than this has been studied in 6 normal subjects by Ebert, Stead and Gibson,¹ and in 27 convalescents by Wallace and Sharpey-Schafer.¹³ Our results confirm many features of these reports. Our studies also included estimations of cardiac output from ballistocardiograms and many observations on the effect-

of the erect position on the signs and symptoms which followed acute hemorrhage. Finally, gaining confidence with experience, certain of the authors volunteered to be bled until serious symptoms were produced, giving us a unique opportunity to study the situation near the breaking-point.

The investigation here reported was initiated by Shenkin, Cheney, Govons, and Starr, and a preliminary report of their results has already been published.⁷ But, as Dr. Govons' work took him to another city, the advantage of his collaboration was confined to the first part of the study. Somewhat later, Hardy and Fletcher, investigating blood substitutes in the same laboratory and with the same apparatus, tried these agents on volunteers subjected to controlled hemorrhage and so obtained data on hemorrhage as a by-product of their greater interest. The detailed report of their experience with blood substitutes will be made later, but their observations on hemorrhage have been included here.

From the data obtained by both these groups, one can draw a picture of the effect of uncomplicated hemorrhage on healthy men. This picture proved to be quite different from our expectations and we hope that our experience may be of use to those charged with the care of soldiers who have bled as a result of wounds.

Technique. The volunteers were chiefly young adult males who believed themselves to be in good health. Those bled 500 cc. usually donated their blood to the hospital blood bank. When larger amounts were withdrawn, after the period of observation, blood volume was restored by using either the blood previously withdrawn or a blood substitute. There were no untoward after-effects of any kind.

After reaching the laboratory, the subjects rested on the horizontal ballistocardiograph for 15 minutes or longer before the first set of observations was made. They were then bled from a convenient antecubital vein into a bottle containing citrate. The bleeding, done under mild suction, required from 4 to 20 minutes. Observations were recorded for varying intervals before restoration of the blood volume.

Cardiac output was calculated from the ballistocardiograms by the area method⁸ and the results have been reported as percentage deviations from the empirical average normal.

Venous pressure was measured through the needle used for the venesection, using a manometer overfilled with citrate solution, the fluid being allowed to run into the vein as far as it would. No reading was accepted unless the top of the column fluctuated with respiration. The error due to resistance in the tubing and needle was estimated and a small correction was applied to the observed values. An imaginary line, parallel to the table and halfway between the anterior chest wall and the table, was employed as a base line.

The hematocrit results were measured on citrated blood in Wintrobe tubes after having been centrifuged $\frac{1}{2}$ hour at 2500 R.P.M. Blood proteins were estimated by a Kjeldahl semi-micro technique. Both these estimations were performed under the direction of Dr. C. Riegel in the Harrison Laboratory for Surgical Research.

The methods of Fisher² were employed in the statistical analysis of certain results. In this paper, the word "significant" is always used in the statistical sense; that is, to indicate that the probability is less than 5 in 100 that the result obtained was due to chance.

The 23 cases studied by Shenkin, Cheney, Govons, and Starr were examined supine and erect, both before and after the hemorrhage. Ballistocardiograms

in the upright position were taken routinely at the beginning of the investigation but, after hemorrhage, most were so distorted by the subject's inability to stand still that cardiac output could not be estimated. We were usually forced, therefore, to be content with estimations of blood pressure and pulse rate when the subjects stood. Hardy and Fletcher's first 9 subjects were studied only when supine; the last 2 were studied in both positions.

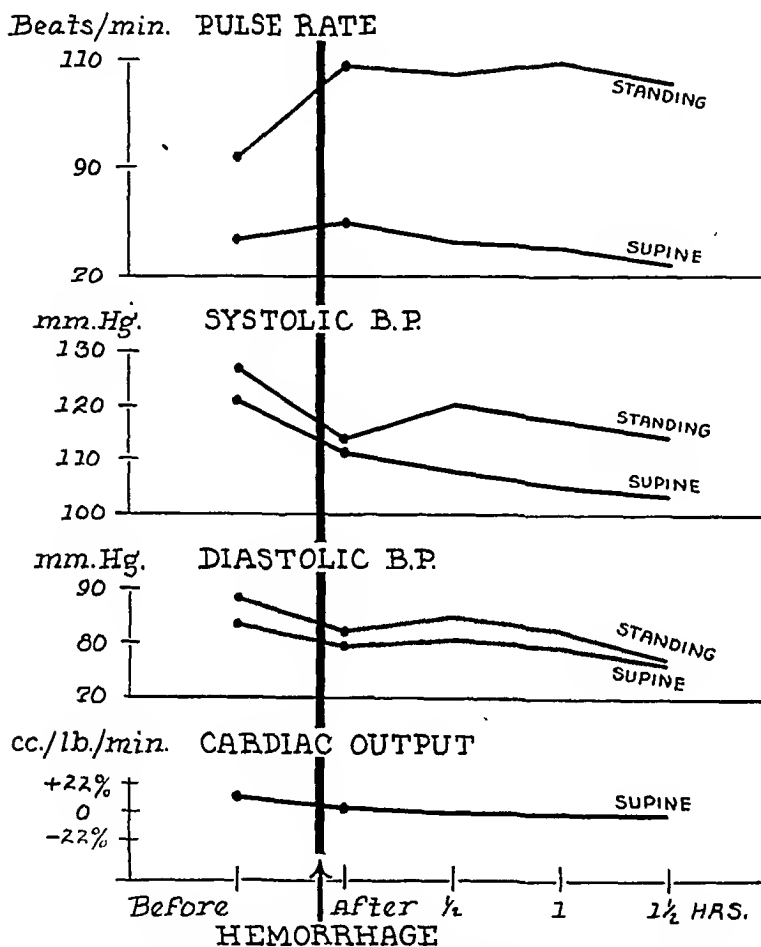


FIG. 1.—Average values found in 18 subjects bled 500 cc. (i. e., from 2.5 to 3.8 cc. per pound body weight).

Results. OBSERVATIONS ON SUBJECTS BLED APPROXIMATELY 500 CC. There were 18 subjects in this group and the amount bled ranged from 2.5 to 3.8 cc. per pound of body weight, or roughly 10% of the circulating blood volume. The average values of all observations are given in Figure 1. In interpreting these results, it must be recalled that anyone about to be subjected to a hemorrhage or other unaccustomed procedure is under psychologic tension which passes off as the event proceeds. The senior author's large experience with medical students given drugs, especially with those given inert solutions when they expected drugs, demonstrates this clearly. The slow downward trend of the average values shown in Figure 1 needs no other interpretation than this.

The *systolic blood pressure*, measured with the patient supine, fell on the average 13 mm. after the hemorrhage, and this is highly significant. But this value was greatly influenced by the results obtained in 2 subjects in whom it fell 48 and 30 mm. and then quickly recovered. There was also 1 subject, evidently much excited, whose systolic pressure, 150 mm. Hg before hemorrhage, fell to normal and remained there after the strain was over. If these 3 cases are omitted, the average diminution was only 9 mm. Hg immediately after the hemorrhage, but this is still significant. There was a slight downward trend for the remaining period of observation.

The average systolic pressure when the subjects stood, differed very little from that found when they were recumbent. The average standing value diminished 14 mm. Hg after the hemorrhage, and this is significant.

In supine subjects the average *diastolic blood pressure* did not change significantly after the hemorrhage; but when the subjects stood, this pressure averaged 7 mm. less after the hemorrhage, and this difference is significant. The average pulse pressure was not changed materially by the hemorrhage.

When the subjects were supine, the average *pulse rate* did not change significantly after hemorrhage of 500 cc.; but when erect, the average increase after hemorrhage was conspicuous and highly significant. This increase was maintained during the period of observation. Before hemorrhage, the average pulse rate increased 15% on arising, a change within the normal range; but immediately after hemorrhage it increased 36%, and 1 hour later 40%, both these values being abnormal.^{9,11} Despite the increase found in the great majority, on 4 occasions the pulse rate in the erect position markedly diminished after the bleeding and all these patients collapsed soon afterwards. The significance of this finding will be discussed later.

The average *cardiac output* and *stroke volume* changed very little after the 500 cc. hemorrhages. These measurements were made only in the supine position, since, when the subjects stood erect after the hemorrhage, there was usually sufficient tremor to ruin the record of the cardiac impacts.

OBSERVATIONS ON SUBJECTS BLED APPROXIMATELY 1 LITER. After hemorrhages of this magnitude, 11 subjects were observed for about $\frac{1}{2}$ hour or under; 5 for 3 hours; and 1 for 24 hours before restoration of blood volume. Records of 2 typical cases are given in Figures 2 and 3, and the data are to be found in Tables 1, 2 and 3.

Hemodilution was followed by means of the hematocrits. In 11 cases (Table 1), samples were taken before and within 25 minutes of the cessation of bleeding; in these the reduction of corpuscle volume averaged 2%. In 3 cases, the samples were taken at hourly intervals after the hemorrhage was over; the reduction at the 1st hour averaged 3.7%, at both the 2nd and 3rd hours, 3.3%. The results obtained on J. D. H., studied for 20 hours, are recorded in Table 2. As expected, a slowly increasing dilution of blood took place after hemorrhage, but

it was far from sufficient to restore blood volume in any of our cases during the period of observation.

Observations Made While the Subjects Were Recumbent. In the great majority the blood pressure diminished after the hemorrhage, but in

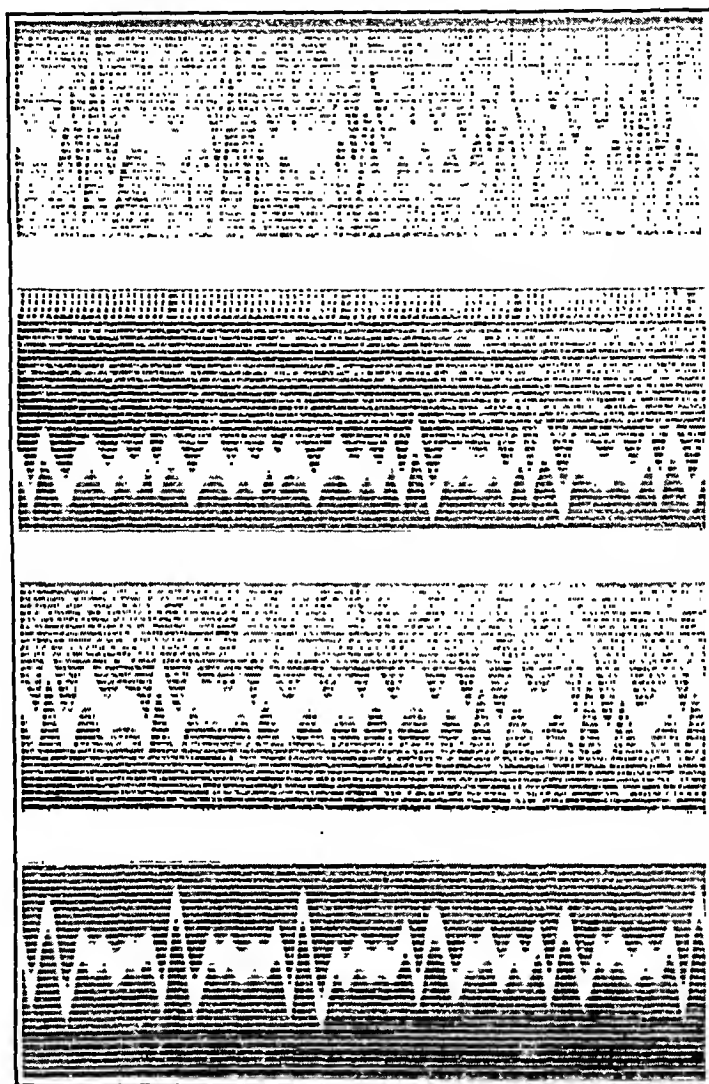


FIG. 2.—Ballistocardiograms on T. D., age 37, ht. 5' 9½", weight 182 lbs.
The reproduction is $\frac{2}{3}$ actual size.

Top record obtained before bleeding at 2 P.M. Pulse rate 75 per min., blood pressure 124/86 mm. Hg. Cardiac output per minute deviates from expected average normal by +13% (normal limits $\pm 22\%$). *Second record* at 3:12 P.M. Pulse 82. B. P. 124/92. Cardiac output -30%. *Third record* at 4:45. Pulse 87. B. P. 120/98. Cardiac output -24%. Between 5:02 and 5:47, 970 cc. of blood was replaced. *Last record* at 6:07. Pulse 82. B. P. 124/90. Cardiac output -9%.

2 subjects it remained essentially unchanged; in 1 it increased somewhat, perhaps due to the involuntary muscular movements occurring at this time. In most cases the minimum was reached just after bleeding had ceased; but in some, it occurred from $\frac{1}{2}$ to 1 hour later.

After the minimum had passed, the blood pressure increased slowly. If first seen 2 hours after the event, the hemorrhage would never have been suspected from the blood pressure readings taken while the subjects lay at rest.

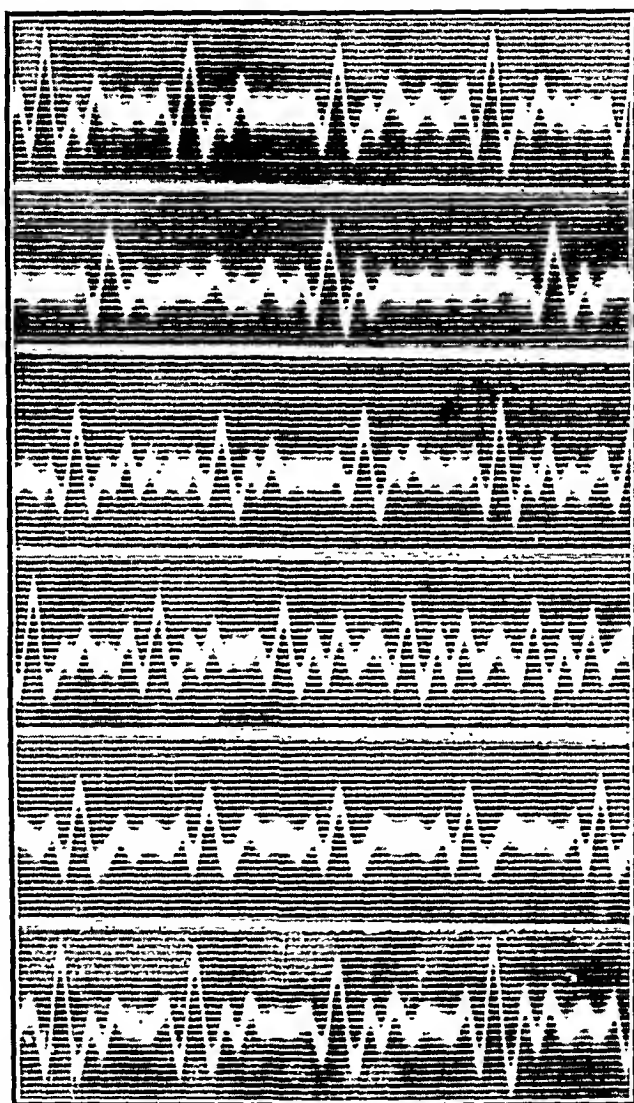


FIG. 3.—Ballistocardiograms on J. J., age 24, ht. 5' 7", weight 137 lbs. The reproduction is $\frac{2}{3}$ actual size.

First record obtained before bleeding at 6:48 p.m. Pulse rate 70, blood pressure 110/68. Cardiac output +4%. Between 6:52 and 7:03, 1090 cc. of blood were withdrawn. *Second record* started at 7:06. While the record was running, the pulse rate diminished from 60 to 46, the cardiac output from -9% to -26%. The blood pressure taken at the end was 92/54. Symptoms of nausea and vomiting, pallor and sweating appeared. *Third record* at 7:10. By this time the symptoms had largely passed off. Pulse rate was 70, B. P. 120/70. Cardiac output -9%. *Fourth record* at 9:30. Pulse 80, B. P. 110/64. Cardiac output did not deviate from the expected normal. Between 9:37 and 10:00, the blood withdrawn was replaced. *Fifth record* at 10:00. Pulse 78, B. P. 124/78. Cardiac output +9%. *Sixth record* at 11:00. Pulse 72, B. P. 120/65. Cardiac output +13%.

The *pulse rate*, after these large hemorrhages, exceeded 100 in no case save the subject who had had a corresponding tachycardia before the event. The rate increased materially in only 3 subjects, and in 2 of these the increase was temporary. In contrast to this, the rate slowed materially in 9 subjects and this was accompanied by symptoms to be described. That slowing of the pulse was more common than acceleration greatly surprised us. In subjects first seen after the event, the hemorrhage could never have been diagnosed from the pulse rate.

TABLE 1.—THE CIRCULATION BEFORE AND JUST AFTER BLEEDING LARGE AMOUNTS; DATA OBTAINED WHILE THE SUBJECTS WERE RECUMBENT

Name and age	Height, weight (lbs.)	Amount	Blood pressure, mm. Hg.	Venous pressure, cm. H ₂ O	Heart rate, per min.	Cardiac output, deviation from av. norm.	Remarks
T. K. 49	5' 9" 185	Before After bleeding 1200 cc. in 15 min.	96/70 84/64	11 12	74 92	— 4% — 9%	
J. A. R. 22	6' 1" 180	Before After bleeding 1065 cc. in 18 min.	128/68 130/70	15 15	66 69	+13% — 4%	
C. T. M. 18	5' 7" 135	Before After bleeding 900 cc. in 10 min.	120/78 58/40	16 12	70 53	+ 4% —13	Sweating, faint
B. B. 38	5' 8" 150	Before After bleeding 1020 cc. in 8 min.	114/60 100/60	14 ..	77 77	+61 +30	
E. T. 38	5' 7" 165	Before After bleeding 1050 cc. in 8 min.	130/80	13 ..	89 45	+22 —39	Fainted (see text)
H. G. 30	5' 8" 151	Before After bleeding 1000 cc. in 20 min.	118/70 68/34	14 9	71 58	+17 0	Slight nausea
R. W. C. 25	5' 8" 196	Before After bleeding 1020 cc. in 15 min.	120/60 120/80	14 12	67 71	—17 —13	
L. J. 27	5' 11" 160	Before After bleeding 1090 cc. in 14 min.	150/80 130/80	17 15	112 111	+48 +48	
W. A. C. 25	5' 10" 167	Before After bleeding 920 cc. in 15 min.	130/80 70/40	74 47	+17 —17	Weak, nausea
A. G. F. 26	6' 2" 170	Before After bleeding 1050 cc. in 17 min.	115/70 96/50	76 52	+11 —23	Sweating, pallor, slight nausea
T. N. 25	5' 11" 152	Before After bleeding 1000 cc. in 15 min.	112/66 123/76	10 ..	76 ..	—4 ..	Unconscious, extremities twitching and moving. Atropine 0.7 mg. I. V., revived rapidly
					60	—15	5 min. later, quiet and conscious
			70/40	10	60	—18	10 min. later

Venous pressure was estimated in only 7 subjects. There was either a small diminution or no change after the hemorrhage. These data are recorded in Table 1.

TABLE 2. - OBSERVATIONS MADE ON J. D. H. (AGE 25; HT. 5'11"; 160 LBS.); BEFORE AND AFTER BLEEDING 1115 CC. OR 15 CC. PER KILO. THE OBSERVATIONS HERE RECORDED WERE ALL MADE WHILE THE SUBJECT WAS RECUMBENT AND AT REST

Time	Pulse rate (per min.)	Blood pressure (mm. Hg)	Cardiac output deviation (%)	Hematocrit (% RBC)	Plasma protein (gm./100 cc.)	Remarks
1.33 P.M.	70	114/74	+13	40.5, 41	6.93	After ½ hr. rest
1.45	Bleeding begins
1.55	84	116/80	500 cc. out
2.04	Bleeding over, 1045 cc. out
2.05	45	96/60	-39	Nausea, sweating, weak, pale and faint
2.10	60	70/40	..	40.5, 39	6.76	Symptoms continue
2.12	76	84/62	Better
2.17	72	98/64	-9	Dry mouth, mild headache
2.34	73	100/68	-4	39, 39	6.61	Drank 200 cc. water
3.34	76	104/68	-9	37, 37	6.36	Feeling well while recumbent
5.34	82	108/70	0	38, 40	6.38	Drank 200 cc. water
6.25	81	After supper, 500 cc. fluid
10.00	81	112/78	+13	36, 36	6.20	..
11.00	After sandwich, coffee and water; 400 cc. fluid
1.20 A.M.	72	110/70	+4	36	6.08	..
1.30	To bed; wakeful, took 180 mg. Na amytal
9.17	80	102/60	..	36.5, 36	6.76	..
12.00	Light lunch
2.13 P.M.	78	110/80	+17
2.30	Up and about
3.30	Replacement of blood started
5.15	1035 cc. blood in and about 100 cc. saline
5.20	68	100/78	+17

TABLE 3.—EFFECT OF ARISING ON SUBJECT J. D. H. (AGE 25; HT. 5'11", 160 LBS.); AFTER LOSING 1115 CC. BLOOD AND AFTER ITS REPLACEMENT

Time	Pulse rate (per min.)	Blood pressure (mm. Hg)	Cardiac output deviation from av. normal	Remarks
2.04 P.M.	Bleeding over 1045 cc. out
3.51	80	110/72	..	Feels well when recumbent
3.53	98	100/74	..	Sitting on edge of bed
3.54	76	Sweating, nausea, faintness forced recumbency
5.45	78	108/70	..	Lying comfortably at rest
5.46	Sat up at edge of bed
5.47	88	90/70	..	Dizzy
5.48	88	70/50	..	Nausea and faintness forced recumbency
1.30 A.M.	72	110/70	..	Lying at rest
1.31	Sitting up
1.32	96	98/74
1.38	88	94/70	..	No unusual sensations
1.40	88	88/64	..	Stood up
1.41	..	70/50	..	Dizzy and faint, forced to lie down
9.17 A.M.	80	102/60	..	Lying at rest
9.18	104	86/70	..	Sat up, no symptoms
9.24	96	96/60	..	Still sitting, no symptoms
9.25	120	90/74	..	Standing
9.29	108	80/64	..	Still standing, no symptoms
2.13 P.M.	78	116/64	+18%	Lying comfortably
2.16	102	100/80	+26%	Standing 2 min., no difficulty
5.10	Blood replaced
5.15	65	100/70	+18%	Lying at rest
5.20	72	100/76	-17%	Standing 2 min.

The deviation of serial estimations of *cardiac output*, calculated from ballistocardiograms, has been carefully studied by Tanner;¹² the standard error of the second estimation being 4.8%. For this reason, if an estimation differs from its predecessor by more than 9.6%, the difference is significant. Therefore, the cardiac output diminished significantly after hemorrhage in almost all our subjects. However,

in only 5 was the cardiac output ever found below the empirical lower normal limit, 22% from average normal, and all these cases suffered from acute symptoms at this time. In the absence of such acute attacks, the estimations of cardiac output would have provided no clear evidence of the preceding blood loss in the great majority of instances.

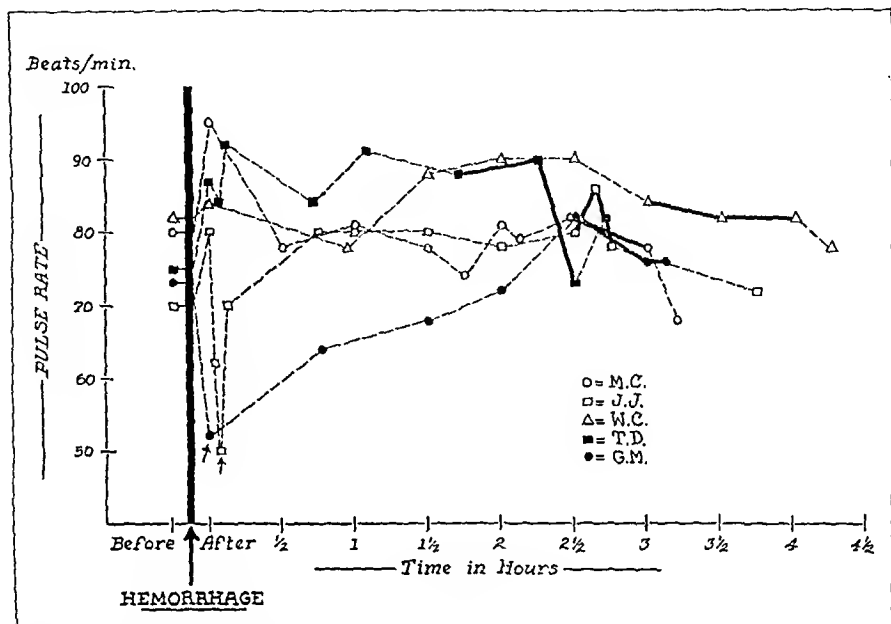


FIG. 4.—Pulse rates taken while the subjects were recumbent and at rest in 5 normal persons, before and after bleeding of approximately 1000 cc., and after replacement of the blood. The heavy line connecting the symbols indicates the period during which the blood was being replaced. The arrows indicate points where the subjects suffered from acute symptoms as described in the text.

Abnormalities Found When, After a Large Hemorrhage, the Subject Arose. In the 6 subjects (see Figures 4, 5, and 6, and Table 3), observations were attempted when they stood erect, as well as when they were recumbent. But the 4 subjects, bled the largest amounts, 5.7, 6.3; 7.0, and 7.9 cc. per pound of body weight, could not tolerate the erect position because of faintness and dizziness, soon followed by collapse, if they were not immediately laid flat. The other 2 subjects, bled smaller amounts in proportion to their weight, 5.3 and 5.4 cc. per pound, were able to stand without collapse, but the abnormal increase in their pulse rates on arising indicated the strain to which the circulation was subjected. Thus in 1 of these cases, the pulse rate before the hemorrhage was 82 recumbent and 93 after arising; the corresponding figures immediately after, and at $\frac{1}{2}$ hour intervals after the hemorrhage, were 84 and 124, 78 and 124, 88 and 112, 90 and 120. In the other case, the pulse rate was 75 recumbent and 86 after arising before the hemorrhage. Immediately after it, these rates were 84 and 96; at $\frac{1}{2}$ hour intervals thereafter, they were 84 and 156, 82 and 156, 87 and 148. After the return of the blood, the pulse rates in the 2

positions closely approximated those recorded before the hemorrhage in both these cases.

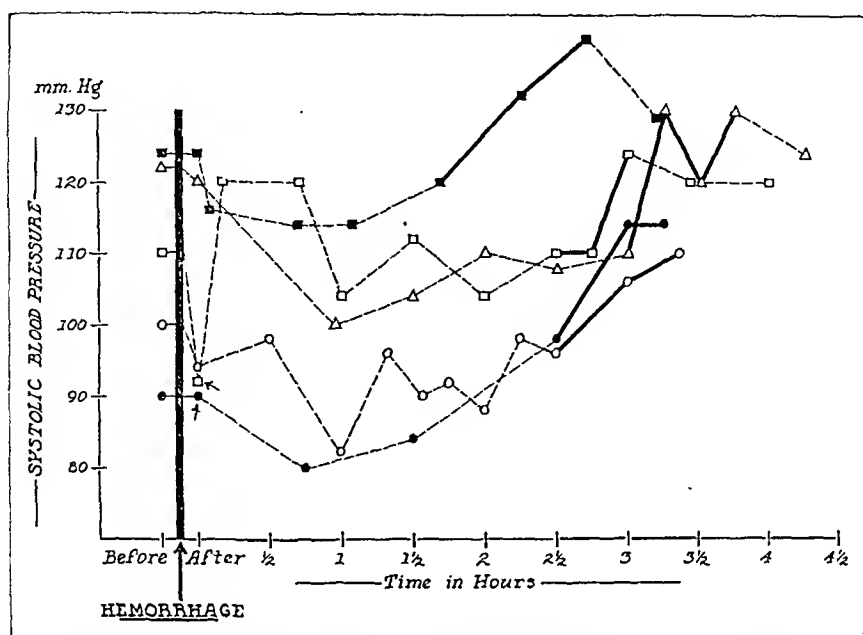


FIG. 5.—Systolic blood pressure of 5 subjects bled approximately 1000 cc. Other symbols as in Figure 4.

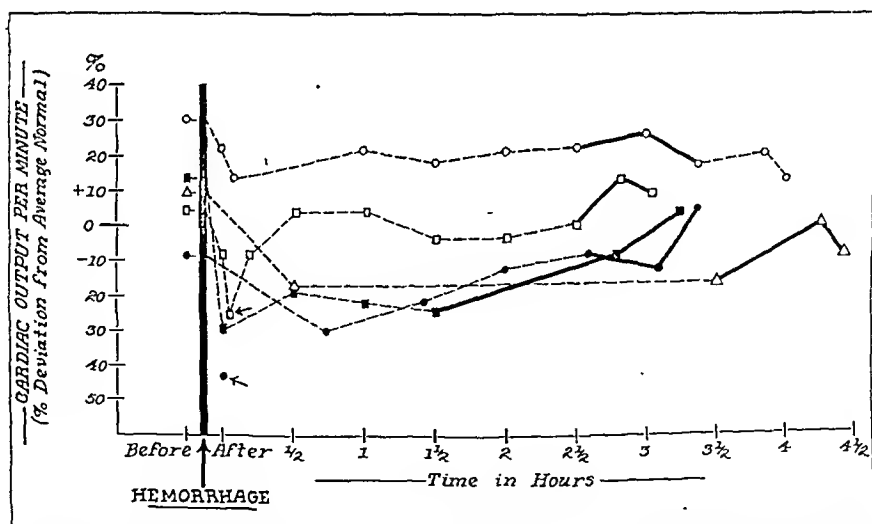


FIG. 6.—Cardiac output per minute, expressed as a percentage deviation from the normal average in 5 subjects bled approximately 1000 cc. Symbols as in Figure 4.

In the 4 who became faint, a sharp acceleration of the pulse was noted immediately after arising but, almost before a count could be made, the pulse slowed markedly and values below 50 were regularly obtained as the symptoms of collapse manifested themselves.

In 2 who did not faint on arising, the *systolic blood pressure*, which before the hemorrhage changed less than 5 mm. when they arose, after the hemorrhage fell, from 10 to 30 mm. Hg in every estimation save 1, when an increase of 6 mm. was recorded. Diastolic pressure in either position was not greatly affected by the hemorrhage in these subjects.

In the 4 who became faint, the blood pressure tended to collapse as the symptoms appeared, but the exigencies of the moment permitted few estimations. The *acute symptoms* which so many subjects experienced when they stood upright, and a few when they lay recumbent, differed only in their severity. The picture will be described in detail under later headings.

Observations on Subject J. D. H., Bled Over 1 Liter and Observed for 24 Hours. After the rest of the studies had been completed, 1 of the authors volunteered for a more exacting experiment. It was planned to bleed him until the production of severe symptoms and then follow the progress of spontaneous recovery for 24 hours. The objective results of this experience are recorded in Tables 2 and 3. These and the subjective sensations which accompanied them deserve detailed description, as the subject was a trained observer.

After control observations, bleeding progressed uneventfully until about 750 cc. had been withdrawn. Then the subject noted waves of tingling going lengthwise over his body and these were soon followed by generalized tingling. Nothing further was noted until after 1035 cc. had been withdrawn. Promptly thereafter, nausea and faintness were noted while vision became dim. The observers now noted pallor, coldness of hands, hyperventilation, restlessness, generalized sweating, bradycardia, and diminished blood pressure. From the record now taken, cardiac output was calculated to be about $\frac{1}{2}$ that found before the hemorrhage. During this period of severe symptoms, the subject noted that his respiratory efforts markedly affected his sensations; hyperventilation improved the symptoms, and as soon as he stopped exerting himself, faintness overwhelmed him. Also he felt forced to keep moving and so flexed his legs and moved them from side to side, because he did not dare to lie still. Finally his hands went into carpal spasm, and the observers demonstrated Chvostek's sign.

After about 5 minutes, the symptoms began to improve spontaneously, the carpal spasm and positive Chvostek's sign persisting longer than the other manifestations. Blood pressure and cardiac output increased with improvement in the symptoms. Finally the subject noted only a dry mouth, thirst, and a mild headache, which gradually passed off. He was then comfortable as long as he lay at rest. During this period, both cardiac output and blood pressure, while lower than before the hemorrhage, were not outside empirical normal limits.

However, when he attempted to sit on the side of the table, the pulse rate first accelerated and then slowed markedly. The blood pressure diminished until it could not be obtained. These objective phenomena were accompanied by sweating and sensations of nausea and faintness which forced him to lie down within a few moments.

The condition of comfort when at rest and horizontal, but inability to sit or stand upright, persisted for about 12 hours, during which he drank 1300 cc. of fluid. Twelve hours after the hemorrhage, he could sit upright without symptoms, but he was still unable to stand.

Eighteen hours after the hemorrhage, the subject could both sit and stand without symptoms and considered himself well enough to be up and about. He was, however, weak and suffered from marked dyspnea on exertion. To the observers, he looked and acted like a sick man. He was able to stand without symptoms; but it is to be noted that the pulse rate increased to over 100 whenever he arose, and that the cardiac output, when he stood, was calculated to exceed the resting value. This condition lasted about 8 hours, or until the blood was replaced. The total amount of blood removed, including the samples taken for analysis as well as the initial bleeding, was 1115 cc.

After replacement of a liter of blood, the subject felt restored to normal. On arising now, the pulse rate was only 72 and he was able to stand without symptoms, although the cardiac output diminished.

Discussion. Our results permit us to describe the signs and symptoms of uncomplicated hemorrhage occurring in healthy men.

After a small hemorrhage, the abnormalities encountered may be described as the *1st stage*. In this, the subject has no symptoms when he is recumbent or standing at rest. However, as soon as he arises, an abnormal increment of pulse rate takes place and blood pressure may diminish abnormally. Such subjects are able to go about their business, but they feel weak and notice dyspnea on exertion.

If the hemorrhage be larger, the condition resulting may be described as the *2nd stage*. In this, the subject still has no symptoms and exhibits no abnormality of the circulation as long as he is recumbent and at rest. But as soon as he sits or stands upright, he is seized by a group of acute symptoms characterized by faintness and syncope and accompanied by bradycardia, the group described in detail below.

If the hemorrhage be larger still, the subject, with very little warning, enters the *3rd stage*, and suffers from acute symptoms while he is recumbent. The observers find diminished blood pressure, marked bradycardia, pallor, sweating, hyperpnea, and restlessness. The subject experiences coldness of the extremities, nausea, dizziness, faintness, and he may lose consciousness.

If bleeding be arrested and spontaneous recovery observed, the subjects pass through the 3 stages in the reverse order.

The clinical picture found in our subjects after hemorrhages of known amount resembles closely that described by Wallace and Sharpey-Schafer,¹³ who studied convalescents bled amounts similar to those we employed. It also resembles in most respects the picture seen by McMichael³ in certain air-raid victims, and in one case of experimental hemorrhage that he reported. Syncopal attacks, such as those we observed, were also reported by Ebert, Stead, and Gibson¹ in a study in which the primary interest was in estimations of blood volume after hemorrhage. The data of the authors who have seen

patients after large hemorrhages of known amount seem to be entirely consistent.

But in contradistinction to these results is the widespread belief that hemorrhage is easily diagnosed by a rapid pulse and a low blood pressure. It is true that the authors recall cases of uncomplicated hemorrhage seen in the clinic who showed marked tachycardia. We are not certain of the cause of the difference between these observations and our results, but we have the impression that these patients had very low hemoglobin concentration. So they were probably seen after dilution of the blood had taken place. Perhaps the tachycardia may have been analogous to that so often seen in cases of severe anemia of any kind. It is to be noted that in none of our volunteers had dilution come near to restoring blood volume.

Be that as it may, our results have clearly demonstrated that large hemorrhages can occur without conspicuous effect on pulse rate or blood pressure; and so, as diagnostic criteria, these signs may be both inadequate and misleading. Three things have probably contributed to the traditional viewpoint. First, a rapid pulse and low blood pressure are characteristic of rapid hemorrhage in anesthetized animals, and this has been demonstrated to generations of medical students. The fact that the unanesthetized animal can stand a much larger loss of blood without undue acceleration of the pulse and diminution of blood pressure⁴ is not so widely known to clinicians. Second, few clinicians have ever seen a hemorrhage in which they had any exact idea of the amount of blood lost, and so they were not in a position to criticize the common view. Third, many hospital cases, hemorrhage is associated with trauma; and that rapid pulse rate and low blood pressure may be associated with shock is beyond dispute.

The mechanism of these parasympathetic-like or vaso-vagal attacks is not entirely clear to us. Syncope is common among blood donors and the fact that it may occur on venepuncture before blood is drawn, or in persons watching blood drawn from others, demonstrates clearly that such attacks may be of emotional origin. Nevertheless, there was absolutely nothing in the demeanor of our subjects to suggest undue emotion. Also there is a direct relationship between the incidence of fainting and the amount of blood drawn. Five of 18 subjects fainted on standing in the group bled 500 cc., while in the group bled 1 liter, 5 of the 7 allowed to stand became so faint that they had to be immediately laid flat. This indicates a mechanism at play in our cases which is not of psychogenic origin. Wallace and Sharpey-Schafer¹³ came to the same conclusion; and the results of Poles and Boycott⁵ also support this view, for in their studies the incidence of syncope in donors bled 540 cc. was double that in donors bled 440 cc.

Evidence from animal experiments suggests that this mechanism is not to be attributed to stimulation of the carotid sinus, but it might be thought of as induced by anemia of the brain; for profound slowing of the heart rate sometimes follows the experimental production of cerebral anemia in certain animal experiments.¹⁰ The cardiac output of our subjects was markedly depressed during these attacks, and it

improved *pari passu* with the symptoms; the circulation through the brain may well have behaved similarly. But whether the bradycardia is cause or effect of the cerebral anemia, our data will not permit us to decide. Starr and Collins¹⁰ observed that signs and symptoms preceded bradycardia in persons about to faint. These observations and the experiments of Weiss *et al.*,¹⁵ who found that persons given atropine still suffered from syncope due to nitrites although bradycardia was prevented, suggest that cerebral anemia is primary. To one of our subjects, who had lost consciousness when bled, 0.6 mg. atropine sulfate was given intravenously. He recovered rapidly; but recovery has been rapid in other subjects not so treated and we feel that no conclusions can be drawn.

It is interesting to recall an old study of the effects of large hemorrhages in man. Our predecessor on the Faculty of this school, Dr. Benjamin Rush, relating his experiences concerning the Yellow Fever Epidemic of 1793, wrote:⁶ "I bled many patients twice, and a few 3 times a day. I preferred frequent and small, to large bleedings in the beginning of September; but towards the height and close of the epidemic, I saw no inconvenience from the loss of a pint, and even 20 ounces of blood at a time. I drew from many persons 70 and 80 ounces in 5 days; and from a few, a much larger quantity. Mr. Gribble, cedar-copper, in Front Street, lost by 10 bleedings a 100 ounces of blood; Mr. George, a carter in Ninth Street, lost about the same quantity by 5 bleedings; and Mr. Peter Mierken, 100 and 14 ounces in 5 days. In the last of the above persons the quantity taken was determined by weight. Mr. Toy, blacksmith near Dock Street, was 8 times bled in the course of 7 days. The quantity taken from him was about 100 ounces."

With regard to the effect of such blood letting, Rush says: "1. It raised the pulse when depressed and quickened when it was preternaturally slow or subject to intermissions. 2. It reduced its force and frequency." These 2 statements are not consistent and evidently the effect varied in different patients, as in our results.

One wonders whether, if our hemorrhages had been larger still, a point would have been reached where the expected signs of rapid pulse and low blood pressure would have appeared while the subject was supine. Our data do not give a positive answer to this question but they demonstrate clearly that a hemorrhage carried to the point of collapse may not be accompanied by any acceleration of the pulse. In 1 subject (E. T., in Table 1), the early stages of the bleeding were uneventful but after 6.4 cc. per pound had been withdrawn, although lying supine, he suddenly lost consciousness and blood pressure could not be obtained. The pulse rate before this emergency had never been recorded as abnormally rapid, and during it the rate obtained from the ballistocardiogram was very slow. Although intravenous medication promptly restored the situation in this case, it is evident that subjects cannot be bled larger amounts with safety, and that hemorrhage can produce an alarming condition without tachycardia either before or during the event.

Obviously, therefore, we have been forced to revise our concept of the clinical picture of acute hemorrhage and of the criteria useful in diagnosing such hemorrhage in persons first seen after the event. But, before continuing this discussion one concept, suggested by previous work¹¹ and strongly supported by the results here described, must be reviewed.

The circulation in a standing subject requires an active mechanism of adjustment to prevent accumulation of blood in dependent parts, and to maintain the supply to the brain. This mechanism is not needed when the subject lies horizontal. For this reason drugs or other agents which influence the circulation in one position may have quite a different effect when the subject is in another. Hemorrhage is but another example of a condition which influences the circulation differently in the horizontal and vertical positions.

With this in mind criteria more adequate to diagnose acute hemorrhage in man can be formulated from our experience. If such hemorrhage is suspected and no signs of it are present while the subject is at rest, he should be placed in the upright position. Then if noteworthy hemorrhage has taken place, an undue acceleration of pulse rate, perhaps with a diminution in blood pressure or the production of a syncopal attack accompanied by bradycardia, will speedily betray the abnormality.

Conclusions. Eighteen volunteers were bled approximately 500 cc.; 17 were bled about a liter. Estimation of pulse rate, blood pressure, venous pressure, cardiac output (ballistocardiograms), and hematocrit were made before and after the hemorrhage, during the process of recovery, and often after replacement of the blood.

Cardiac output diminished very little after the loss of 500 cc. of blood; after the loss of a liter, it regularly diminished significantly, and during syncopal attacks, it diminished profoundly. After completion of the bleeding, the cardiac output slowly returned toward the value found before the hemorrhage.

The effects of hemorrhage on healthy men may be divided into 3 stages of severity. In the *1st stage* the subject is symptom-free at rest and has a pulse rate and blood pressure within normal limits. However, on arising, an undue acceleration of pulse rate and some diminution of blood pressure are found. In the *2nd stage* there are still no noteworthy abnormalities as long as the subject is recumbent and at rest. But the upright position cannot be tolerated and syncope soon overwhelms the subject if he arises. In the *3rd stage* syncopal attacks accompanied by bradycardia occur even though the subject is at rest and recumbent. These attacks seem to be of physiologic and not of emotional origin.

The old concept that acute hemorrhage can be readily diagnosed by a rapid pulse and a low blood pressure is erroneous. Recumbent subjects may be bled to the point of collapse without exhibiting conspicuous tachycardia, and during the period of severe symptoms profound bradycardia is the rule. The blood pressure usually remains

within the normal range until the symptoms of collapse begin, when it diminishes profoundly.

Hemorrhages causing no signs or symptoms as long as the subjects are recumbent can be detected by having them sit or stand upright. Then the symptoms described above will speedily betray the abnormality.

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THE EFFECT OF ARTIFICIAL RESTRICTION OF ACTIVITY ON THE RECOVERY OF RATS FROM EXPERIMENTAL MYOCARDIAL INJURY*

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ALTHOUGH rest in bed is the most widely used method of treatment in patients with acute myocardial disorders, there have been practically no well-controlled clinical or experimental studies concerning its value and its limitations. Present practices in the use of this method of treatment are therefore based not on scientific data but on opinions which vary widely as to the length of time during which rest should be enforced, and as to the degree to which it should be applied. Thus, in Table 1 are summarized the opinions expressed by 10 authors as to the duration of rest following myocardial infarction. Some authors believe that 2 or 3 weeks is sufficiently long for the average case, whereas others think that rest in bed for a number of months is necessary. There is a similar lack of uniformity concerning the strictness of the regime of rest, some authors believing that a patient should not

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be allowed to turn in bed, to feed himself, or even lift his head, whereas others hold that even in the acute stage it is permissible for a patient to get out of bed for a bowel movement.

TABLE 1.—OPINIONS OF VARIOUS AUTHORS CONCERNING THE OPTIMAL DURATION OF REST IN BED IN PATIENTS WITH MYOCARDIAL INFARCTION

Author	Duration of bed rest recommended for average patient	Remarks
Meakins ²⁰	"Many weeks or even months"	
Eggleston ⁷	"Many weeks"	Patient should not be allowed to feed himself or turn himself
Clendenning and Hashinger ³	Prolonged period	
Lewis ¹⁷	At least 8 weeks	All voluntary movements to be avoided
Beckman ¹	8 weeks	Turning and feeding should be forbidden for 6 weeks
Smith ²³	6 to 8 weeks	Often longer
Harrison ⁹	6 to 8 weeks	Elderly patients should be allowed out of bed several hours daily after 2 weeks
Christian ²	6 weeks	
Dressler ⁵	6 weeks	Much longer period when attacks of pain persist or blood pressure remains low
Leaman ¹⁴	6 weeks	
Levine ¹⁵	4 to 8 weeks	
Fishberg ⁸	4 to 8 weeks	Prolonged rest especially important in younger patients
Dry ⁶	4 to 6 weeks	Elderly subjects with favorable progress allowed up after 2 to 3 weeks
White ²⁵	4 weeks	Longer periods of bed rest impair morale
Mallory, White and Saleedo-Salgar ¹⁹	4 weeks	
Reid ²¹	Minimum 2 to 3 weeks	Optimal period of bed rest not yet known
Levy ¹⁶	Until infarct has healed	Sedimentation rate and electrocardiograms provide guides to healing
Libman and Sacks ¹⁸	Until leukocyte count is normal	
Hyman and Parsonnet ¹²	Until leukocyte count is normal	Patients who become irritable with bed rest should be allowed up early

Experimental attempts at enforcing artificially induced rest on animals has not been hitherto attempted, insofar as we are aware. The effect of exercise on animals with acute myocardial injury was studied by Sutton and Davis,²⁴ who ligated a coronary artery in 6 dogs and observed the effects of exercise carried out on a treadmill. They found

that in the animals which began severe exercise within 3 days after the ligation, the scar which finally developed was thin and that there was a tendency toward formation of aneurysm of the left ventricle. On the other hand, in the single dog which did not undertake work on the treadmill for 6 days after the production of the cardiac infarct, the scar was firm, small, and well contracted without any thinning of the ventricular wall.

The observation that severe exercise begun as early as 6 days after the injury did not seem to impair the healing process in dogs is at variance with the usual practice of having patients with myocardial infarction remain in bed for many weeks. However, there is some evidence that the heart of the dog may heal more rapidly than that of man. Thus, Karsner and Dwyer¹³ observed in dogs that experimental infarcts were nearly completely healed by the end of 3 weeks. Mallory, White and Salcedo-Salgar¹⁹ studied the hearts of 72 patients in whom the date of onset of infarction was clearly defined from the history. They found that the small infarcts in the human hearts were almost completely healed at the end of 5 weeks; whereas the large infarcts did not reach a similar degree of healing until about 2 months had passed. They believed that the fact that nearly twice as long was required in the case of human hearts as in the case of the dog hearts for a similar degree of fibrosis and healing to take place could be accounted for by the larger size of the human hearts—and hence the larger size of the infarcts—and also by the greater abundance of collateral circulation in the normal dogs than in the patients with coronary sclerosis. A third possibility, namely, that the faster rate of healing in the dog was related to the greater activity of this animal was not considered.

The question of how long an individual should be kept at rigid bed rest following infarction or other acute injury to the heart is important, not only from the standpoint of the heart itself, but from the economic aspects, and perhaps especially from the viewpoint of the patient's morale and mental attitude. A final answer to this question can only be obtained by the controlled study of many hundreds of patients. However, something can be learned by the investigation of problems of allied nature in experimental animals, and it is with this approach to the problem that the present communication is concerned.

Method of Study. In order that a large enough series of animals might be employed so that the results would have statistical significance, rats were used in preference to larger animals. At first, attempts were made to ligate the coronary arteries but these were not successful. Consequently, the following technique was employed.

Under ether anesthesia the chest was opened by an incision through the left fourth interspace over the point of cardiac impulse. The ribs were quickly retracted by means of sutures previously placed around the rib above and the rib below the point of opening. The heart was pushed out through the incision by pressure on the chest. Three to five areas on the left ventricular surface near the apex were burned by the application of the head of a ten-penny nail heated almost to redness. The heart was then replaced and pressure exerted to expel as much air as possible from the chest. The incision was quickly closed by tying the sutures about the ribs. With practice it became possible to carry out the entire procedure from the time the chest was opened

until it was closed again within a period of about 30 seconds. The operative mortality at first was 60 to 70 %, but with further practice this was reduced to 10 to 20 %.

The rats surviving the operative procedure were divided into 2 equal groups, of which 1 was placed in small wire cages especially constructed so that they fitted fairly snugly around the rat. These small "straight-jacket" cages were constructed from "hardware cloth." It was found that for a 200-gm. rat a cage having an external diameter of 6 x 2 x 2 inches was of approximately the correct size, so as not to interfere with the animal's breathing, but at the same time to hamper markedly any movements. In the earliest experiments the animals which were to be later placed in these small cages were first trained by being put in them for a few hours on several successive days prior to the operation. However, later this practice was abandoned when it was found that the rats always tended to struggle somewhat for some few minutes when first put in the cages and then tended to remain rather quiet. Precautions were taken to see that the animals confined in these small cages had access to as much food and water as they desired.

The control animals were treated similarly except that they were put back into large stock rat cages, each of which held several rats. After periods of time varying from as short as 2 weeks in one experiment, to as long as 5 to 7 weeks in most of the experiments, the rats confined to the small cages—hereinafter to be called the "restricted rats"—were taken out and put in the usual stock cages. Notes were made daily concerning the general demeanor of the 2 groups of animals and their apparent clinical condition; autopsies were done on the animals that died.

In order to obtain quantitative data concerning the relative amount of activity of the restricted rats as compared to the control, another series of experiments was carried out and the activity was recorded by an apparatus similar to that devised by Tainter *et al.*²² A wire cage large enough to hold 2 rats comfortably was suspended by a spring and 3 Harvard work adders were attached so as to record the motion of the cage in 3 different planes. An automatic record of the number of revolutions of the work adders was obtained by attaching to each one a string which wound around the axle of the recorder as it revolved. Thus, it was possible to measure the activity of the 2 animals in the suspended cage in terms of revolutions of the 3 work adders. With this apparatus the 2 rats could be left free in the suspended large cage or confined within the smaller "straight-jacket" cages placed within the larger suspended cage. Observations were made on normal rats and also on animals which had been subjected to cardiac injury, the latter rats being usually free in the large cage for 1 day, confined in the small cages for the 2nd day, and alternated in this fashion for a number of days. In this way it was possible to gain an idea as to how much confinement in the small cage did in fact restrict the activity of the rat.

In a 3rd series of experiments the rats were not confined but were allowed to choose their own activity by the use of the optional treadmill.* This apparatus consists of a small cage large enough to allow the rat to move around freely, but not large enough to allow space for much exercise. The cage is connected to a treadmill by a door which remains open. The number of revolutions of the treadmill are recorded on a small Veeder counter. The animals in this series of experiments were first made accustomed to the apparatus by being placed in it for a number of days prior to the chest operation. Following production of cardiac injury the animal was put back into the apparatus and the daily number of revolutions of the treadmill was noted.

In a 4th group of experiments the effect of forced exercise was studied. The heart was injured by burning in the usual way, and one or more days after this procedure one-half of the animals were forced to swim for varying periods of time. In order to separate the effects of exercise from those due to the wetting and chilling of the skin, the control animals were dipped in the water and

*. This apparatus was obtained from the Geo. H. Wahmann Mfg. Co., Baltimore, Md.

taken out without being allowed to swim. The mortality and the rate of healing of the hearts in the control and the swimming animals were then compared.

Results. 1. *The Effect of Restriction of Activity on the Mortality Subsequent to Cardiac Injury.* In this series of experiments 142 rats were used. Of these, 46 died during or immediately after the operation

EFFECT OF RESTRICTION OF MOVEMENT ON SURVIVAL OF RATS
FOLLOWING EXPERIMENTAL MYOCARDIAL INJURY

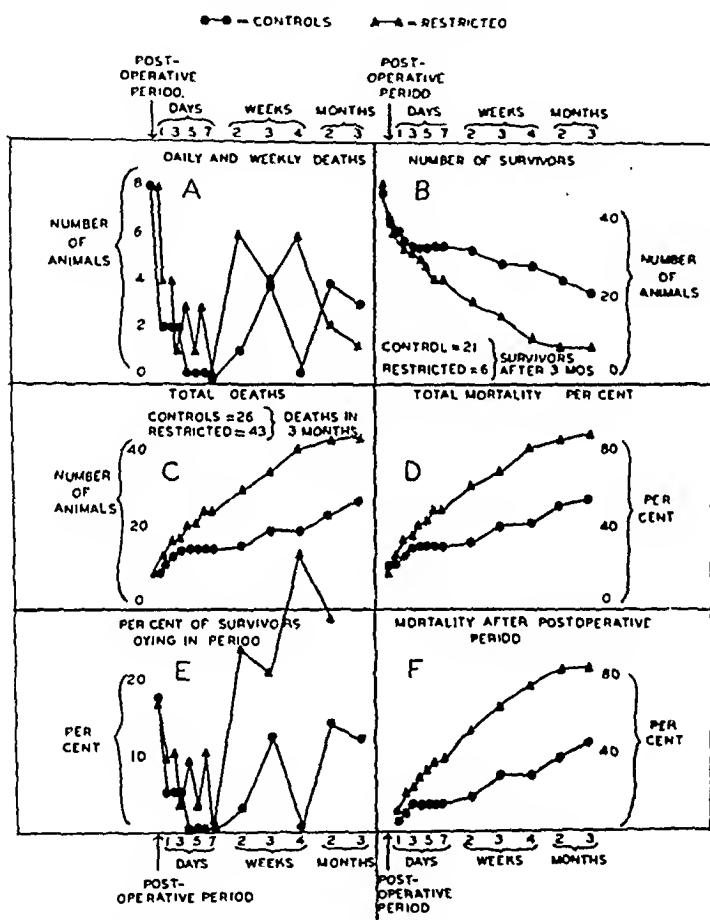


FIG. 1.—A, During the 1st month the number of deaths in the restricted animals (triangles) tended to be considerably greater than in the controls. The apparent decrease in mortality in the restricted animals during the 2nd and 3rd months is due to the small number of survivors in this group. B, C, D, E, These curves all emphasize the greater mortality in the restricted group. F, Elimination from consideration of the deaths occurring during the immediate postoperative period indicates that the difference in mortality due to restriction is really greater (F) than the difference in total mortality (D).

on the heart. The remaining 96 rats consisted of 47 controls and 49 restricted animals. The data concerning mortality and survival in these 2 groups are shown in Figure 1. The mortality in the post-operative period, which was arbitrarily taken as the time from the end of the operation until 9 o'clock the next morning, was the same in

the 2 groups, 8 animals dying in each during this period. In all subsequent periods the mortality was greater in the confined group, the difference being consistent and of rather striking degree. Thus, at the end of 3 months there were only 7 survivors out of the original 49 rats in the restricted group, and of these 7 survivors 5 were animals which had been removed from the "straight-jacket" cages 2 weeks after the operation. On the other hand, 21 of the 47 controls operated on survived the 3-month period. Similarly, the total number of animals dying in 3 months was 42 in the restricted group as compared to 26 in the controls. If the deaths during the postoperative periods are omitted from consideration, which would seem justifiable because such deaths were obviously related to the operative procedure rather than to the method of treatment, we are left with a total of 34 deaths in the restricted animals and 18 deaths in the controls.

Observations of the appearance of the 2 groups of rats were of some interest. Most of the animals in the control series who survived the first 2 days seemed to regain their strength and appetites rapidly, and these tended to assume the sleek and alert appearance of a normal rat. The restricted animals appeared unhappy, apathetic and asthenic. They tended to lose weight slightly, while the controls gained or remained constant.

The autopsy findings in these rats will not be discussed in the present communication, as these will form the subject of a separate report in which an attempt will be made to compare the rate of healing of wounds in the rat and in man, as well as the rate of healing of the hearts in the different animals with which this communication deals. Here it only need be stated that most of the deaths in the period immediately after operation were the result of hemorrhage from the heart, and that later deaths were due to infections in the thoracic cavity, pneumonia, cardiac rupture and, oftentimes, to unknown causes.

2. *The Total Daily Activity of Restricted and of Control Rats.* Observation of the rats confined in the small cages showed that from time to time they tended to struggle somewhat, but that this became less after the rats had been in the cages for a few days. The activity, as measured by the recorder, showed a very striking difference between animals confined in the small cages and those left free to wander at will in the larger cages (Fig. 2). The total number of revolutions of the work adder was usually 10 times as much in the case of the latter group. Thus, it is clear that the somewhat heroic straight-jacket method of producing restriction of muscular movement did in fact limit the activity, and to a very striking degree.

3. *The Spontaneous Activity of Rats Following Burning of the Heart.* In the experiments as previously described the rats have been artificially restricted in their movements and the animal had no opportunity to make a choice. Hence, it seemed desirable to carry out a group of experiments in which the animal would be free to exercise or not, as desired, and in which the amount of exercise carried out could be compared after the operation with that prior to it, in order to deter-

mine how long a time elapsed before the rat tended to assume his pre-injury activity level.

The results of these experiments were rather surprising and are shown in Figure 3. Even following rather extensive searing of the ventricular surface each rat returned to his preoperative level of exercise in 3 to 7 days, the average being approximately 5 days. One is forced to

EFFECT OF CONFINEMENT IN SMALL CAGES ON 24 HOUR ACTIVITY OF RATS

(EACH CURVE = TOTAL ACTIVITY OF 2 RATS)

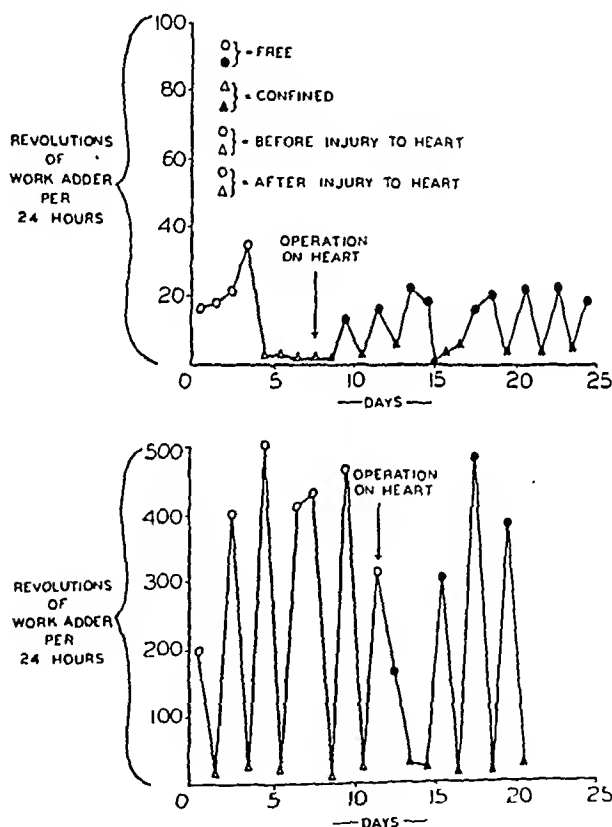


FIG. 2.—The results show that whether normal rats (hollow symbols) or rats with injured hearts (solid symbols) are employed, confinement in the small cages did result in well-marked decrease in the 24-hour activity. Although the method used is not entirely adequate for the purpose desired, the differences in activity, as measured, are so great as to seem well beyond any reasonable likelihood of error.

assume either that (1) the rat deliberately undertakes a level of activity which is physically harmful; or (2) that such early resumption of normal activity is not harmful. In order to attempt to distinguish between these 2 alternatives, additional experiments were done.

4. *Effect of Strenuous Exercise on the Mortality Following Myocardial Injury.* (See Table 2.) They would seem to indicate that strenuous

exercise is perhaps harmful when begun within the first 48 hours after injury to the heart. However, after that period of time there is little difference in the mortality in the 2 groups. Some of the early deaths were unexplained at autopsy and may have been the result of ventricular fibrillation. An analysis of the deaths caused by cardiac rupture

SPONTANEOUS ACTIVITY OF RATS ON OPTIONAL TREADMILL

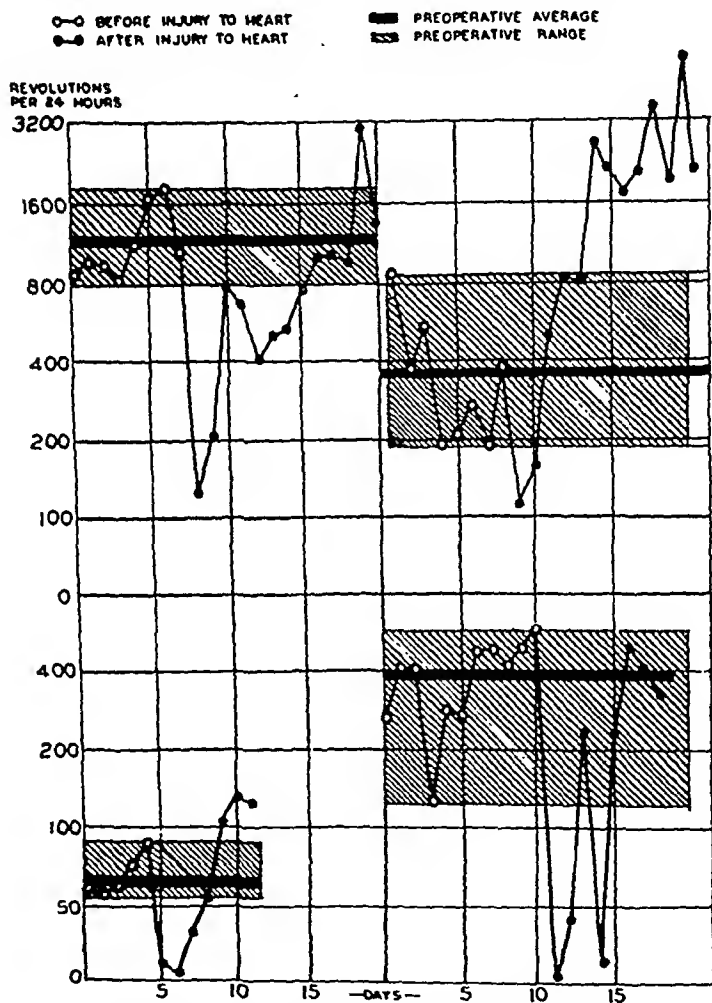


FIG. 3.—No compulsion was employed, the animals being free to follow their own desires both in the preoperative and postoperative periods. Two points are of interest: (a) No rat chose to avoid exercise entirely, even on the 1st postoperative day. (b) The general tendency was toward a marked reduction in exercise during the 1st 48 hours after cardiac injury with a return to (or above) the preoperative level of activity within 3 to 7 days.

is interesting. The period of time from the 5th to the 15th postoperative day was found to be the optimum period of development. None of the animals suffered this accident while in the act of swimming or within 6 hours following cessation of the exercise. Rupture occurred later in the animals forced to exercise than in those which were not exercised. The importance of factors other than exercise *per se* is

emphasized by the study. Further investigation of these problems is being carried out.

TABLE 2.—THE EFFECT OF SWIMMING ON THE MORTALITY OF RATS WITH MYOCARDIAL DAMAGE
(The letters indicate a death occurring on that day)

		Postoperative day															
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Controls (11 rats)	No swimming			I							R						
Exercised	Amount of exercise: 10 minutes 3 times a day																
Group 1 (10 rats)	Begun 1st postopera- tive day and contin- ued <i>every</i> day there- after	U	I				I										
Group 2 (11 rats)	Begun 3rd postopera- tive day and contin- ued <i>every other</i> day thereafter			U												R	
Group 3 (10 rats)	Begun 5th postopera- tive day and contin- ued <i>every 3rd</i> day thereafter				I				R							R	

Key to letters:

I indicates death due to infection.

U indicates that no cause of death was found at autopsy.

R indicates that death was due to cardiac rupture.

Note: At the end of 45 days of the experiment no more deaths had occurred.

Discussion. The data which are presented seem to have established the following points: (1) Under the conditions of these experiments, immobilization of the animals caused a pronounced increase in the mortality following injury to the myocardium. (2) Such immobilization was accompanied by a well-marked restriction of activity. (3) When the animals were allowed to follow their own desires they deliberately chose to resume a normal life—as regards physical exercise—within less than a week after the cardiac injury. (4) When rats had been allowed to rest for as short a time as 3 days following severe injury to the heart, the mortality was not significantly increased by having them carry out strenuous exercise for 10 minutes 3 times a day. In view of these findings it seems justifiable to conclude that—in the case of the rat at least—prolonged restriction of activity following cardiac injury is not only not beneficial, but actually harmful.

There are a number of reasons why one is not justified in drawing any direct conclusions concerning patients from these experiments. First of all there is the species difference. In the second place, the type of injury induced is artificial and does not bear close resemblance to that occurring in disease, even in a condition such as myocardial infarction which is likewise accompanied by focal injury to the heart. Third, the rats were young and in excellent health prior to the cardiac injury, a condition which obtains only in a minority of the patients with myocardial infarction. Fourth, the rate of the healing process

in the heart of the rat is probably much faster than in that of man. Finally, the artificial conditions of restricted activity in the animals do not bear a close resemblance to rest in bed of patients, but are more analogous to the use of a straight-jacket. Granting the validity of these points of dissimilarity between the experimental results presented in this communication and myocardial infarction in man, the data would seem to us at least to justify an attitude of skepticism con-

TABLE 3.—THEORETICAL EFFECTS OF REST IN BED ON FATAL COMPLICATIONS OF MYOCARDIAL INFARCTION

Complication	Probable effect of prolonged bed rest on the likelihood of its occurrence	Remarks
Ventricular fibrillation	Decrease	Quinidine perhaps more important than absolute rest; no evidence concerning optional position
Rupture of heart	Decrease	{ These complications are very rare after the end of 2nd week; recumbent posture tends to prevent
Acute circulatory collapse	Decrease	
Renal insufficiency	Decrease	
Systemic embolism	Decrease	May occur many months later
Ventricular aneurysm	Decrease	No evidence concerning optional position
Further myocardial infarction	Increase	Both spread of original thrombus and formation of new ones favored by prolonged rest
Pulmonary edema	Increase	Sitting position tends to prevent
Pulmonary embolism	Increase	Failure to move legs favors thrombosis in veins
Pneumonia	Increase	{ Elderly subjects confined to bed from any cause tend to develop these complications
Cerebral thrombosis	Increase	
Prostatic obstruction	Increase	

Note that those complications which tend to be prevented by absolute rest usually occur within the first 2 weeks—while the complications which are favored by bed rest tend to occur later.

TABLE 4.—THEORETICAL EFFECTS OF PROLONGED REST IN BED ON SUBSEQUENT MORBIDITY OF PATIENTS SURVIVING MYOCARDIAL INFARCTION

Complication	Probable effect of prolonged bed rest on the likelihood of its occurrence	Remarks
Angina pectoris	Uncertain	Anginal attacks are more frequent in recumbent than in sitting position
Congestive failure	Uncertain	Recumbency aggravates congestive failure when present
Further myocardial infarction	Increase	Mild activity increases coronary flow and probably tends to prevent thrombosis
Cardiac neurosis	Increase	The longer the period of absolute rest the greater the psychic trauma

cerning the desirability of prolonged and extreme bed rest in patients. It therefore seems worth while to consider certain theoretical aspects of this question.

The various complications which are the common causes of death in patients with myocardial infarction, as well as those which are likely to occur subsequently in patients who survive this disorder, are summarized in Tables 3 and 4 and the probable effect of prolonged rest in bed as the likelihood of their occurrence is indicated. It seems probable that ventricular fibrillation, rupture of the heart, acute circulatory collapse and renal insufficiency due to diminished blood pressure are less likely to develop if the patient is kept rigidly in bed in the recumbent position. However, it should be noted that these complications tend to occur in the first 2 weeks and are rare after this time.

It seems probable that prolonged rest would tend to prevent the development of ventricular aneurysm. Whether this complication would tend to develop more readily in the sitting than in the recumbent position is uncertain. In most patients the blood pressure is somewhat higher sitting, but all who have studied the subject agree that the cardiac output is 5 to 20% greater in the recumbent than in the sitting position. The work of the heart per minute might therefore be greater in the one position in some patients and in the other position in other patients. Since the pulse rate is somewhat faster in the sitting position, it is probable that the work per beat, and hence the amount of energy developed at each contraction, is greater in the recumbent posture. From this point of view one might expect that the development of ventricular aneurysm would be more likely to occur in a recumbent than in a sitting patient, both of whom were remaining at rest in bed.

As regards peripheral embolism resulting from ventricular mural thrombosis, the studies of Mallory, White and Salcedo-Salgar¹⁹ make it seem probable that this complication would be most likely to occur in the first 2 weeks. They found that mural thrombosis often begins early and that the thrombus is frequently completely organized by the 16th day. However, they found in other subjects that thrombosis might occur weeks or even months following the infarction. Since it seems probable that a patient walking around out of bed would be more likely to produce an embolus than a person remaining quietly in bed, it would seem that for the purpose of the prevention of this complication a period of bed rest lasting several months would be indicated. The question arises, however, whether in view of the relative rarity of this complication one would be justified in keeping all patients in bed for such a prolonged period in order to prevent embolism in an occasional patient. Since, as will be pointed out in succeeding paragraphs, prolonged rest in bed has a number of important disadvantages, it would not seem, on the basis of theoretical considerations, that such a plan of treatment is desirable. In some patients, and perhaps in the majority, the development of mural thrombosis leads to certain manifestations, including slight fever, a

persistent leukocytosis and sustained increase in the sedimentation rate. One might therefore take the position that in cases who still display these abnormalities at the end of a 2- to 3-week period a longer period of rest in bed is indicated than in the usual instance.

There is a series of important complications of myocardial infarction which are likely to develop late, that is, after the first 2 or 3 weeks. These include additional infarction as the result either of formation of new clots in a different vessel, or the spread of the original clot, acute pulmonary edema, pulmonary embolism from silent thrombi in the vessels of the legs, bronchopneumonia, cerebral thrombosis and difficulty in urination which may at times progress to anuria. On theoretical grounds one would expect these complications to develop more readily in persons remaining recumbent in bed than in individuals who are either allowed to sit up in bed, or perhaps, better, allowed to sit in a chair and walk around a slight amount each day. Without having statistics to strengthen the opinion, I have the impression that this second group of complications causes more deaths in patients with coronary thrombosis than does the first group of conditions, which usually occur early and which probably are less apt to occur in patients kept in bed in the recumbent posture. On theoretical grounds, then, one can logically take the position that, generally speaking, a patient with myocardial infarctions should be kept in bed for a period of 2 to 3 weeks, being allowed to sit up in bed the 3rd week, and after that being allowed out of bed for very slowly increasing periods of time. The desirability of such a plan of management is far from established on the basis of available evidence. However, it seems reasonable, in the light of the considerations which have been mentioned.

When we turn from those conditions which tend to cause death during the initial illness to the conditions which are apt to occur as late complications in individuals who have recovered from the acute myocardial infarction, we likewise encounter further uncertainty concerning the desirability of prolonged rest in bed. Whether a patient who is kept strictly in bed for only 2 weeks following myocardial infarction is more apt or less apt to have angina pectoris in the future than a similar patient who has been in bed for 3 months is uncertain. In favor of prolonged bed rest is the fact that it should theoretically allow more time for the uninjured muscle to take on an additional load. Even a slight increase in the oxygen requirement of the heart might tend to induce angina in a patient where the balance between oxygen need and oxygen supply was finely adjusted. On the other hand there is considerable evidence that exercise in moderation tends to benefit patients with angina pectoris. Thus, Heberden¹¹ cited a patient who was nearly cured following several months during which he undertook the task of sawing wood for $\frac{1}{2}$ hour daily. Connor⁴ likewise has emphasized the value of exercise in patients with angina pectoris, and we have believed for a long time that those individuals with this disorder who remained moderately active (but below the pain threshold) were more apt to improve than the patients who restricted their activities to an absolute minimum. Probably, physical activity with a slight

increase in the metabolism of the heart tends to increase the collateral circulation through the healthy coronary branches. In any case it is worth emphasizing that patients who are at rest are much more apt to have anginal attacks in the recumbent than in the sitting posture,¹⁰ and hence that from the standpoint of preventing the anginal attacks a patient who is to be subjected to prolonged bed rest should be allowed to be in the sitting posture several hours a day, at least after the first 2 or 3 weeks following infarction.

As regards congestive heart failure, which is the ultimate cause of death in a large percentage of the people who have had myocardial infarction, it is well known that the upright position favors the development of edema in the legs, while the recumbent position favors the development of edema in the lungs. Since the latter is more serious than the former it would seem again that there is an advantage in having the patient sit up rather than lie down in bed.

The likelihood of the development of additional myocardial infarction has already been discussed, and here again it seems probable that a moderate amount of activity, with the attendant increase in coronary flow, would tend to prevent the formation of thrombi in the vessels.

One of the most common complications of myocardial infarction is cardiac neurosis. Every experienced physician has seen many patients in whom the disability due to the patient's anxiety and fright causes far more suffering than the actual cardiac disease itself. The longer a patient is forced to stay in bed and the more he is impressed with the dire consequences which may follow the premature resumption of activity, the more likely he is to develop a cardiac neurosis. This point is not an inconsequential one because it is just as important for the physician to prevent mental suffering as to prolong physical life. The theoretical disadvantages of strict rest in bed in the recumbent position can be overcome in large measure by allowing a patient to sit up in a chair several hours a day and perhaps to walk a few steps in a gradually increasing regimen. We know of no evidence which is contrary to the idea that the activity of patients should be restricted for many weeks following infarction. The question is not whether restriction of activity is desirable but rather whether *prolonged rigid* restriction is desirable.

A strict régime of rest in bed has 2 components. One of these is decrease in the metabolic rate of the body and presumably of the heart as well; the other is muscular immobilization. It is the latter which has been studied in the present communication and the data show very clearly that such immobilization is quite harmful. In the case of the rats confined to the "straight-jacket" cages the degree of immobilization is greater than in the case of the patient kept rigidly in bed, and perhaps the degree of metabolic reduction is less. Under the conditions in which our experiments were carried out it is clear that any advantages resulting from decreased metabolic rate were far outweighed by the harmful effects of muscular immobilization. Whether or not this is true in patients with acute myocardial injury is unknown. If one makes the reasonable assumption that decrease in metabolism is

desirable in such patients, there are still no accurate data on the question of how this objective may best be achieved. The patient who is not dyspneic presumably has a lower metabolic rate lying down than sitting up. However, in the patient with even a mild degree of orthopnea the reverse is probably true. Data are needed concerning the relation of defecation to this problem. The respective metabolic increments induced by using a bed pan and a bedside commode should be investigated. Similarly, observations concerning the oxygen consumption during unhappy recumbency *versus* satisfied sitting are desirable. Until information of this type is available it is well for us to bear in mind that prolonged bed rest following myocardial infarction has serious psychic disadvantages. The physical advantage to a patient of rest in bed for a period longer than 2 weeks is as yet unproven. The available evidence derived from morbid anatomy would suggest that rigid rest for a period of 1 month to 6 weeks may be desirable. The evidence obtained from experiment would perhaps suggests that confinement in bed for a period this long is undesirable. A final answer can only be derived from a critical and careful study of many hundreds of patients. Until such a study has been carried out, we would maintain an open mind about the question, realizing that while there are advantages there are also disadvantages in keeping a patient rigidly in bed for a prolonged period.

Summary. Following experimental injury to the hearts of rats the mortality is decidedly greater when the animals are kept closely confined in small cages which restrict muscular activity.

Animals so confined display considerably less activity, as measured by the work adder method, than control animals allowed to wander freely about in larger cages.

Observations with the optional treadmill have shown that following injury to the heart the rat tends to return to the preoperative level of exercise within a period of 3 to 7 days.

Enforced strenuous muscular effort even when carried out within 24 hours after cardiac injury, did not materially increase the mortality in rats. Likewise, such exercise carried out 3 or more days after the operation did not cause a significant increase in mortality.

The question of the desirability of prolonged and rigid rest in bed following myocardial infarction in patients has been discussed and it has been pointed out that this procedure has serious disadvantages as well as some advantages. On the basis of the available evidence it would appear that during the first 2 weeks the advantages of strict bed rest probably outweigh the disadvantages, but that after this time the reverse is probably true.

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ALLOXAN DIABETES IN THE RABBIT

A CONSIDERATION OF THE MORPHOLOGIC AND PHYSIOLOGIC CHANGES

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THE production of diabetes in experimental animals by the injection of alloxan has evoked general interest and discussion. This drug has a specific effect on the pancreatic islets of Langerhans and thereby produces diabetes within 24 hours. The relation, if any, between alloxan diabetes and human diabetes immediately presents itself and this question is being intensively studied at the present time.

That alloxan, when injected intravenously into rabbits, may produce a fatal hypoglycemia was first recorded by Jacobs¹⁵ in 1937. Since

only the gross pathology was studied, the islet changes were not recognized. Dunn, Sheehan and McLetchie⁶ were the first to stimulate widespread interest in alloxan when they reported a selective necrosis of the islets of Langerhans following intravenous injection into rabbits. The majority of these animals "died during the 1st day or so with distinctive symptoms, which were not referable to renal disease." In several animals they noticed a low blood sugar shortly before death.

Bailey and Bailey,¹ reviewing these data, considered the hypothesis that with destruction of the islet cells there might be a massive release of insulin. Hence these animals could be dying in hypoglycemia. Further, if hypoglycemic death could be prevented, then with extensive destruction of the islets the animals should develop diabetes. Support for this hypothesis was gained by the fact that hypoglycemic death was prevented by the repeated administration of intravenous dextrose, and diabetic animals were obtained within 24 hours.

Brunschwig, Allen, Goldner and Gomori³ report "sustained hyperglycemia" in 5 dogs observed for 2 to 3 weeks, and "transitory hyperglycemia" in rabbits following alloxan. Three human patients with carcinomatosis, one arising in the islets of Langerhans, were also given alloxan intravenously but no immediate effect was obtained. Later Brunschwig, Allen, Owens and Thornton* gave a subsequent report upon the patient with carcinomatosis arising in the islets of Langerhans and stated that temporary symptomatic relief from hypoglycemic attacks for brief periods of 10 to 20 days, followed each series of alloxan injections.

Dunn, Kirkpatrick, McLetchie and Telfer⁴ discussed in detail the pathologic findings in the rabbits and reported permanent hyperglycemia with similar pancreatic lesions in the rat following alloxan. They described a ring of intact cells at the periphery of the islets and suggested that these might be alpha cells. Dunn and McLetchie,⁵ in describing alloxan diabetes in the rat, emphasized the fact that in this animal the kidneys were also not infrequently damaged. Diabetic acidosis and coma in the rat have also been observed.

The dog with alloxan diabetes was first carefully studied by Goldner and Gomori⁸ who noticed a remarkable specificity of the dosage. Single doses exceeding 100 mg. per kg. caused death within a few hours. A dose between 75 and 100 mg. per kg. produced a diabetic uremic syndrome with death within 1 week. A dose of 50 to 75 mg. per kg. produced typical diabetes without renal lesion. Doses of 25 mg. per kg. were without effect. Guinea pigs, cats and pigeons were likewise given alloxan but without the production of permanent diabetes. By differential stains they showed that on the 3rd day after injection only alpha and non-granular cells remained.

Studying the rat, Gomori and Goldner¹² found nuclear pyknosis of the beta cells 3 hours after the injection of alloxan. Hooded rats, they found, were resistant to this drug. Hughes, Ware and Young,¹⁴ however, report changes in the beta cells 5 minutes after the subcu-

* BRUNSWIG, A., ALLEN, J. G., OWENS, F. M., JR., and THORNTON, T. F.: J. Am. Med. Assn., 124, 212, 1944.

taneous injection of alloxan into rats. They were able to reproduce in the rabbit the hyperglycemia-hypoglycemic blood sugar curve that follows alloxan by injecting adrenalin and simultaneously the amount of insulin, as protamine zinc insulin, that would normally be present in the rabbit pancreas.

Goldner and Gomori⁹ showed that the initial hyperglycemia following alloxan can be prevented with insulin and the subsequent hypoglycemia by dextrose injection; yet the beta cells will degenerate and diabetes develop.

Bailey, Bailey and Leech² found that diabetic cataracts developed within 1 to 3 months in rabbits and rats kept alive with alloxan diabetes. Small repeated injections were tried, and whereas 20 mg. per kg. have failed to produce diabetes when given 3 times a week for 2 months, a larger dose of 40 mg. per kg. daily produced diabetes after 8 and 14 injections respectively. In the 2 rabbits with the larger dosage, certain islet cells presented a clear-cut picture of hydropic degeneration. Mitosis was also seen in several cells. In the islets some changes were reversible and some irreversible. They found 200 mg. per kg. subcutaneously the most effective dose for the rat, as 15 of 18 rats given this dose developed diabetes.

Hard and Carr¹³ emphasize cytoplasmic vacuolation in the adrenal medulla in addition to destruction of the islets of Langerhans in the rabbit made diabetic with alloxan.

Goldner and Gomori¹⁰ recently showed that destruction of the adrenal medulla prior to alloxan injection prevented the initial hyperglycemic phase and that animals who had been made diabetic with alloxan or pancreatectomy failed to develop marked hypoglycemia after alloxan injection. Furthermore, insulin assay of the pancreas from 3 dogs made diabetic with alloxan showed only 0.5 unit per gm. as compared with the normal of 2 to 3 units per gm. of pancreas.

Thorogood¹⁸ injected 50 rats subcutaneously with 200 mg. per kg. of alloxan. Ten developed diabetes, 10 were not affected and 30 died.

A detailed summary of the literature can be found in a recent Diabetic Progress article by Joslin.¹⁶

The purpose of this paper is: (1) to correlate and report in detail the pathologic findings in the pancreas and other organs of the rabbit at varying intervals after the intravenous injection of 200 mg. per kg. of alloxan; (2) to discuss the diabetic complications which have occurred in this animal, as well as those looked for but not found; and (3) to discuss the physiology of the blood sugar changes following the injection of alloxan.

Since the blood sugar values uniformly pass through 3 stages—transitory hyperglycemia, transitory hypoglycemia and permanent hyperglycemia—a study has been carried out to determine at what time the cells of the islets of Langerhans first show morphologic changes, whether the alterations seen microscopically are the same or different in each stage, and whether processes in the islet cells seem to represent a continuous effect. For these studies the rabbit has been used as the experimental animal. In spite of its numerous shortcom-

ings as a test species in the laboratory, the ease of intravenous injection, the possibility of repeated blood chemistry determinations and the facility with which alloxan diabetes is produced have recommended it for these experiments.

Materials and Methods. All rabbits used in these experiments have been either Dutch or Chinchilla strains.

In the early experiments a 2% aqueous solution of alloxan was given intravenously in 3 separate injections at 15 minute intervals for the production of diabetes. Later a single injection of a 5% aqueous solution of alloxan was used with equivalent results. The total diabetogenic dosage was 200 mg. of alloxan per kg. of body weight. Smaller doses, as specified below, were used for the production of transitory diabetes. Only freshly prepared solutions were used. The alloxan used was kindly supplied by the American Cyanamide Company.

Blood sugars were taken from the ear vein by the capillary method and determined by the micro procedure of Folin and Malmos.⁷ Smith's¹⁷ modification of Benedict's method was used for the determination of the percentage of glycosuria.

The diet throughout the investigation consisted of rabbit pellets which contain carbohydrate 63%, protein 13%, fat 3% and fiber 12%. These pellets contained adequate vitamins and minerals.

On the day of injection the rabbits, which had been fasted overnight, first had 2 control blood sugar samples taken. Immediately afterward, the alloxan was injected slowly. Blood sugar samples were thereafter taken at 15 minute intervals for the 1st hour and 30 minute intervals thereafter until a convulsion occurred. The hypoglycemic convulsion was relieved with 2 cc. of 50% dextrose intravenously, and thereafter the rabbits were allowed to eat. This prevented further convulsions. Every rabbit given alloxan in this way was diabetic within 36 hours.

In nearly all cases insulin was begun on the 3d day, since by this time the blood sugar level usually approached 400 mg. and frequently diacetic acid had appeared in the urine.

The animals were sacrificed, usually by air embolism, at various intervals, as indicated in the discussion of the results. Autopsies were performed immediately, the pancreas being the first organ removed. Routine fixation was in Zenker's fluid with phloxine and methylene blue staining of the sections. For studies of the granules of the islet cells, blocks of pancreatic tissue were fixed in Bouin's fluid and sections stained with Gomori's method for these structures.¹¹

The Islets in the Phase of Initial Hyperglycemia. For the study of the pancreas in this phase, material of 2 types was prepared. The first of these consisted of 3 rabbits, each given 200 mg. per kg. of alloxan in a single injection administered over a period of 10 minutes. One was sacrificed $\frac{1}{2}$ hour after the end of the injection, 1 after 1 hour, and 1 after 2 hours. The phloxine and methylene blue stain was used. For study of other intervals and of the rôle played by the different types of islet cells, 3 rabbits were anesthetized with nembutal, $\frac{1}{2}$ gr. per kg. subcutaneously 1 hour preoperatively, and sufficient nembutal intravenously immediately before operation to produce surgical anesthesia. Less than $\frac{1}{4}$ gr. per kg. was required. The abdomens were opened and a biopsy of the normal pancreas taken. Alloxan, 200 mg. per kg., was then injected intravenously in 10 minutes. Successive biopsies were taken as follows:

Rabbit No. 1. Normal, 15 minutes, 30 minutes, 1, 2, 4 and 6 hours after the end of the injection.

Rabbit No. 2. Normal, 10, 15, 30, 45 and 60 minutes after the end of the injection.

Rabbit No. 3. Normal, 5, 15, 30 and 60 minutes after the end of the injection.

The specimens were fixed in Bouin's solution and stained with Gomori's granule stain.¹¹ The specimens of the pancreas removed before the injection of alloxan corresponded to published descriptions.¹¹

In the specimen secured 5 minutes after the injection of alloxan, the nuclear membranes of many islet cells, especially the beta cells, were more prominent and their cytoplasm was rather clear with some loss of granules. These changes, though slight, were definite and indicate the speed of localization of alloxan in the islet cells.

At 10 and 15 minutes, the alpha cells appeared normal but most of the granules had disappeared from the cytoplasm of the cells at the centers of the islets. The nuclei were essentially the same as at 5 minutes.

At 30 and 45 minutes the central cells were somewhat more closely packed than in previous specimens, their nuclei were more shrunken, but the chromatin was still granular. The cytoplasm of these cells was still intact in outline but there was further loss of granules. Numerous normal alpha cells were seen.

In specimens at 1 hour and 1½ hours, the nuclei of the central cells were further shrunken and the chromatin formed a compact deeply staining mass. Their cytoplasm had become less dense and early cytoplasmic disintegration was apparent in some areas. The capillaries were congested.

At 2 hours, these processes had extended further, and distortion of the general architecture of the islets was more clearly indicated than at shorter intervals after the administration of alloxan.

These findings indicate that degenerative changes begin in the islet cells very quickly after the injection of alloxan and progress steadily toward the fully established lesion associated with diabetes. At no stage was neutrophil infiltration seen and the stroma, blood-vessel walls and pancreatic parenchyma remained unchanged.

The Islets in the Phase of Hypoglycemia. Four rabbits were sacrificed during the phase of hypoglycemia (at 3, 4, 5 and 6 hours after the end of the injection). There were also available 2 biopsy specimens from Rabbit No. 1, described above.

Three hours after the end of the injection of alloxan, the islet cells showed a somewhat further progression of the processes described in the preceding section. The islets were somewhat swollen. The nuclei of the majority of the islet cells were pyknotic, being composed of homogeneous masses of very deeply staining chromatin. The cytoplasm was irregular in outline and took the phloxine stain strongly. The cells displaying these changes were separated somewhat from one another. Certain other cells located largely at the periphery of the islets were very well preserved. These appeared to be alpha and non-granular cells, no normal beta cells being encountered. No infil-

tration with polymorphonuclear leukocytes or wandering cells was seen. The blood-vessels, stroma and acinar tissue were normal.

In the rabbit sacrificed 4 hours after injection and in the biopsy at 4 hours (as described in the previous section) there was further progression of the changes in the islets of Langerhans. The cells with pyknotic nuclei and degenerating cytoplasm had coalesced somewhat, so that the individual islets were smaller than at 3 hours. The number and distribution of cells which had not undergone degeneration was unchanged.

At 5 hours after injection and in the biopsy 6 hours after alloxan administration, the coalescence of the islet cells had progressed further and the number of degenerated cells in each islet was smaller. This was interpreted as an indication that some of them had disintegrated completely. By the end of 6 hours, more of the affected cells had disappeared without infiltration of polymorphonuclear leukocytes or wandering cells. The number, character and distribution of the morphologically normal cells were the same as in rabbits sacrificed at shorter times.

The lesions in the period of hypoglycemia, then, were regarded as a progression of changes which began very quickly after the injection of alloxan. There was no alteration in the character of the lesion which could be correlated with the rapid drop in blood sugar. At the height of the period of hypoglycemia, the lesion was approaching that which was found in the diabetic phase.

The Islets in the Phase of Diabetes. Fifteen rabbits were studied histologically in the phase of diabetes. Two of these were sacrificed 1 day after injection, 4 at 3 days, 1 at 4 days, 3 at 12 days, 1 at 14 days, 1 at 20 days, 1 at 3 months, 1 at 5 months and 1 at 5½ months. There was also available material from 1 rabbit whose pancreas was biopsied at 3 days and again at 84 days after the injection of alloxan.

In the rabbits sacrificed within 3 weeks after the onset of diabetes, the remnants of the islets were very inconspicuous. Compared with the normal islet of Langerhans in a control rabbit (Fig. 1) the islet 3 days after the injection and 2 days after the onset of diabetes showed that all the degenerating cells had disappeared, whereas the cells unaffected by the alloxan retained their previous morphology (Fig. 2). The islet was somewhat collapsed and flattened. In the central portion the stroma cells remained intact and no inflammatory cell infiltration was noted. It is likely that some islets had disappeared entirely, for they seemed to be less numerous than in control sections, and occasional small mats of fibrous tissue in the usual position of islets were interpreted as islets of which only the stroma remained. Thus, the lesion of fully developed alloxan diabetes could be characterized as a loss of all beta cells with persistence of small numbers of alpha and non-granular cells in the absence of detectable injury to the external secreting tissue of the pancreas.

The rabbits sacrificed 2, 2½, 5 and 5½ months after injection had remained diabetic. They had been maintained in good general condition by the administration of adequate doses of insulin. All had,

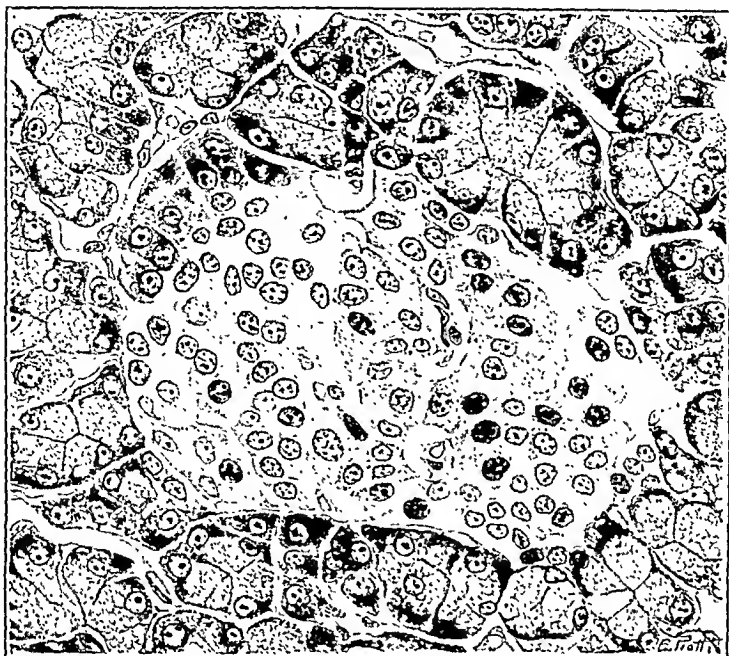


FIG. 1.—Islet of Langerhans in the pancreas of a control rabbit. (Camera lucida $\times 1300$, reduced.)

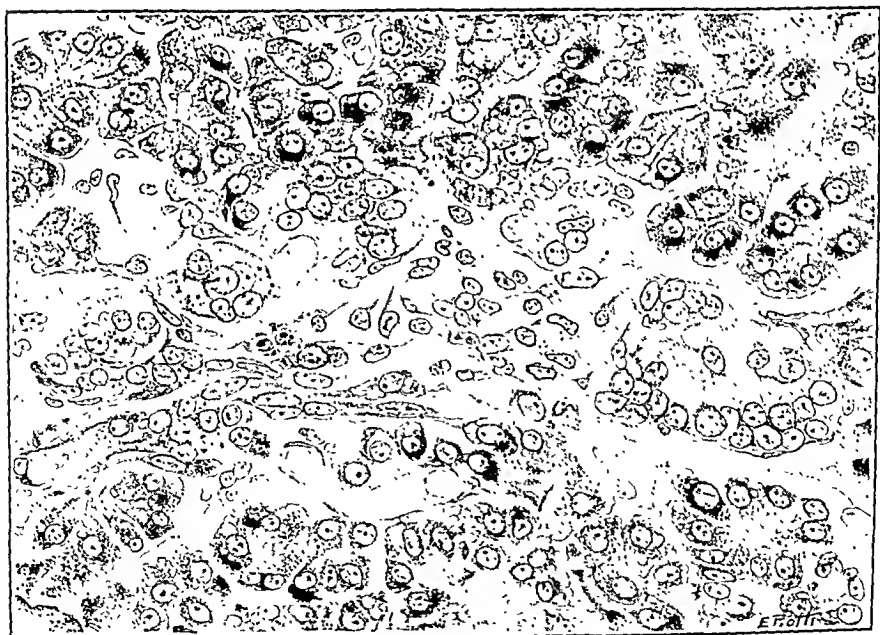


FIG. 2.—Islet of Langerhans of a rabbit 3 days after the intravenous injection of alloxan. The rabbit had well-established diabetes. The functional cells at the center of the islet, including all the beta cells, are destroyed, though the stromal cells persist. There is no inflammatory cell infiltration. The few preserved functional cells at the periphery are alpha and agranular cells. (Camera lucida $\times 1300$, reduced.)

however, developed cataract. In this period there was one biopsy at 84 days after injection.

The findings in the pancreas in the animals allowed to survive for several months after the establishment of diabetes by means of alloxan was confined to the islets. The total number of islets was small, suggesting that some of them had disappeared without leaving any trace. Those which survived were composed of masses of cells resembling alpha cells as far as could be judged by phloxine and methylene blue stain (Fig. 3). The pancreas of 1 rabbit sacrificed at 3 months, and the biopsy material were stained by Gomori's method. In these 2 specimens, the cells were wholly alpha cells and confirmed the impression obtained from histologic sections prepared by routine methods. No beta cells could be identified. The number of cells in these islets was greater than the number surviving at 3 days after the injection of alloxan. It appeared probable, therefore, that there was some proliferation of the alpha cells, though no mitoses were seen in any of the rabbits receiving 200 mg. per kg. of alloxan.

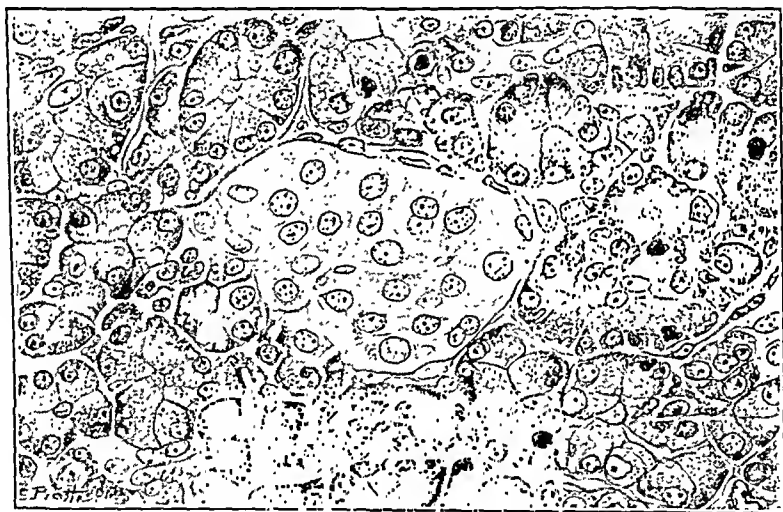


FIG. 3.—Islet of Langerhans of a rabbit 2 months after the intravenous injection of alloxan. Diabetes was present 24 hours after the injection and persisted to the time of sacrifice. The islet consists of a group of alpha cells without any beta cells. (Camera lucida $\times 1300$, reduced.)

The Islets in Diabetes Induced by Small Doses. As pointed out in a previous publication,² the repeated injection of 40 mg. of alloxan per kg. in rabbits over a period of 2 to 3 weeks induced a gradual rise of the blood sugar. After the injections were stopped, the blood sugar fell toward normal, indicating that the lesions were reversible from the physiologic point of view. We now have 3 rabbits which were sacrificed after the second blood sugar value of 200 gm. per 100 cc. was obtained. The lesion in the islets of Langerhans differed in many respects from that induced by large single doses of alloxan. Many types of alteration were encountered in the cells. Some of them

appeared entirely normal. Others had lost their specific granules; still others showed a few small vacuoles. In some, there was typical hydropic degeneration similar to that described in pituitary diabetes. Occasional cells displayed irreversible changes, as judged by loss of the nucleus. Scattered mitoses were encountered, but in no instance more than 1 per islet (Fig. 4). Many islets showed no mitoses. In none of the sections was there inflammatory cellular infiltration.

This type of alteration in the islet cell of the pancreas was striking and it would be difficult to match it among the well-recognized lesions of islet cells. It suggests that different cells receive various degrees of injury by the small doses of alloxan. From the standpoint of morphology of the individual cells, some of these changes are reversible, while others are irreversible, the former predominating. There is some

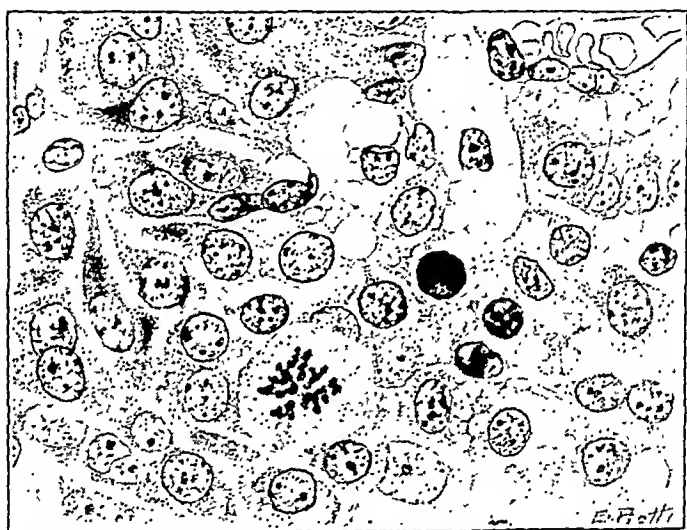


FIG. 4.—A portion of an islet of Langerhans of a rabbit developing mild diabetes after repeated injections of alloxan, 40 mg. per kg. The cells show a variety of changes. Some are essentially normal. Others show various degrees of hydropic degeneration. One is in mitosis. (Camera lucida $\times 1300$, reduced.)

replacement of irreversibly altered cells, as indicated by the mitoses. This is in conformity with the observation that the diabetes is physiologically reversible. In these islets, there was no scar formation and no inflammatory cellular infiltration. The acinar tissue appeared entirely normal.

Changes in Organs Other Than the Pancreas. The changes in organs other than the pancreas appear to be minimal. Our findings are in conformity with those which have been published elsewhere.^{4,5, etc.} In the rabbits sacrificed within 3 days after the injection of 200 mg. per kg. of alloxan the kidneys showed a mild degeneration of the tubular epithelium. This consisted of vacuolization and some desquamation of the cells. The glomeruli appeared essentially normal. In rabbits sacrificed at longer periods after injection, there were no lesions which could be definitely correlated with the administration of alloxan,

though the rabbit is a poor experimental animal for the exact interpretation of minor renal lesions. The slight evidence of morphologic change in the kidney correlates well with the absence of changes in non-protein nitrogen of the blood.

In rabbits sacrificed within 3 days after the injection of alloxan, some of the liver cord cells showed mild fatty metamorphosis, but no massive necroses were seen. The livers of rabbits sacrificed from 2 to 5 months after injection appeared entirely normal.

Sections of all the endocrine glands were studied in each of the animals. These studies included the pituitary. All these tissues, with the exception of the pancreas, appeared within the range of normal. There was some congestion of the vessels in and about the adrenal in the animals sacrificed within the first 24 hours. This change did not seem sufficiently constant or striking to permit the statement that it was beyond the possible range of normal animals sacrificed in the same way. While evidence has been published that the adrenal gland plays a rôle in the physiologic changes,¹⁰ we find it difficult to regard any morphologic alteration which we have seen as a reflection of this activity.

Histologic sections of other organs showed no lesions due to the injection of alloxan.

Diabetic Complications. It has been shown elsewhere^{1,2} that diabetic coma results in certain animals—both rats and rabbits—unless the diabetes produced by alloxan is controlled by the administration of insulin. We did not find any histologic changes which were to be correlated with the development of diabetic coma in these animals, although exhaustive cytologic studies of the brain were not undertaken. The technique of alloxan diabetes, however, could be well used in making such study.

The development of cataracts has also been described in another paper.² As discussed there, the development of cataracts as viewed by slit-lamp corresponded in all respects to the development of cataracts in human individuals. Histologically also the cataracts corresponded to the picture of human diabetic cataracts. Cataracts seem to develop much more quickly and progress further in rabbits with poorly controlled diabetes than in those receiving insulin.

None of the rabbits so far studied presented evidence of arteriosclerosis. The rabbit is so prone to spontaneous arteriosclerosis that it would seem an unsuitable animal for the evaluation of the relation of diabetes to arteriosclerosis. This would be true even though the percentage of such lesions was to prove high in rabbits which had been maintained in diabetes over a considerable period of time. No physiologic changes suggestive of diabetic neuritis have yet appeared and no degeneration of peripheral nerves was noted in histologic sections.

Comment. This study, as well as numerous investigations in the literature, indicates that the most striking characteristic of the lesion induced by the injection of alloxan is the specificity which it shows for the islets of Langerhans. Furthermore, the beta cells are affected

most severely and a certain percentage of the alpha cells remains intact. This specificity not only provides an excellent technique for the production of diabetic animals in the laboratory but also presents a problem in the correlation of chemical and morphologic relationships. The changes outside the pancreas are minor in character from the morphologic point of view. This is a further indication of the specificity of alloxan for the islets of Langerhans, and also provides evidence that the animals may be maintained for long periods of time by the administration of insulin without complicating extrapancreatic lesions. From the point of view of the investigator, however, it is unfortunate that the alpha cells are not completely destroyed. Experimental pituitary diabetes can result in destruction of beta cells without destruction of alpha cells. It would be useful if, in alloxan diabetes, there was complete destruction of the islet cells, so that a preparation would be available with the external secreting parenchyma intact but all cells of the islets destroyed. Alloxan, however, does not satisfy these requirements.

There are conspicuous species differences in the extent of extrapancreatic lesions induced by the injection of alloxan. For instance, the lesion of the kidney in the rat², and others is much more severe than are those in the rabbit. The studies reported in this paper indicate that the lesion of the islets of Langerhans after the injection of alloxan begins its development a very short time after the injection has been given and continues in a steady progression to the fully established lesion. There is no break in the sequence at any point. The lesion is degenerative from the beginning and progresses through a stage of almost complete destruction to one of repair by cells which are unable to secrete insulin. For this reason, the explanation for the hypoglycemic phase must be sought elsewhere than in a stimulation of the islets of Langerhans. It seems to us likely that the initial hyperglycemic phase has an extrapancreatic origin and the experiments of Goldner and Gomori¹⁰ indicate clearly that the adrenal is connected with this phase.

The lack of cellular response to the necrosis in the islets of Langerhans is remarkable. In almost all other forms of necrosis, neutrophils may be seen at one stage or another. The response of the islets of Langerhans to alloxan, therefore, offers a biologic problem of considerable interest from the standpoint of general pathology.

The lesions induced by small doses of alloxan are very striking. The number and variety of changes in the islet cells are not reminiscent of any well-known lesion of these islets. For comparable lesions, one is inclined to look for comparison more toward the early sequences in other organs following administration of certain carcinogenic hydrocarbons than to the lesions produced by massive doses of alloxan or to those recognized in human diabetes.

From these considerations, it appears that the injection of alloxan not only provides a useful technique for obtaining diabetic animals in the laboratory and for the study of diabetic complications, but also

provides a useful technique for the study of numerous problems in general pathology.*

Summary. A study of the lesion induced by alloxan at numerous intervals in the islets of Langerhans of the rabbit, indicates that it begins almost immediately after the injection of the material and that it is degenerative from the beginning. Degenerative changes in the islet cells are already apparent in the initial hyperglycemic stages, and in the hypoglycemic stage they progress to a point where they approach those of the diabetic phase. The histologic lesions in the different phases of the blood sugar curve are one continuous process. The pancreatic acini remain normal throughout and changes in organs other than the pancreas are minimal.

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ACUTE YELLOW ATROPHY OF THE LIVER IN EARLY SYPHILIS

A CASE REPORT WITH SUMMARY OF THE LITERATURE

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ACUTE yellow atrophy of the liver occurring in early syphilis is very rare. Its incidence as a complication of acute, *untreated* syphilis is

* Since this paper was submitted for publication, there has appeared a study relevant to this discussion. (Ridout, J. H., Ham, A. W., and Wrenshall, G. A.: Science, 100, 57, 1944.) This investigation showed by means of insulin assays and histologic studies on the pancreases of rats and dogs after administration of alloxan that "the insulin content of the pancreas did not fall appreciably until after most islet cells were found by histological examination, to be dead. . . . It appears most unlikely that it exerts its hypoglycemic effect by stimulating islet cell secretion because most of the islet cells are dead when the hypoglycemic phase occurs."

There is thus evidence from physiologic and morphologic studies that alloxan causes hypoglycemia by release of preformed insulin. The hypothesis suggested in our first studies¹ thus receives strong support from two entirely independent investigative techniques.

small, although it is seen more frequently following arsenical therapy. Therefore it seemed worthwhile to report this case, in which jaundice occurred accompanying secondary syphilis, progressing in a few weeks to acute yellow atrophy.

Jaundice occurring in syphilis was noted as early as 1585 by Paracelsus.²⁹ It was early appreciated that hepatic involvement in acute syphilis might take one of two forms—relatively benign syphilitic hepatitis or grave icterus, a fulminating acute yellow atrophy. Herxheimer¹³ estimated that the incidence of jaundice was 0.3 to 3% of all patients with early syphilis. In 1853 Gubler¹² proposed as proof for the syphilitic etiology of this jaundice the five points: (1) that it exists in the absence of other common causes of jaundice; (2) that it coincides with other specific symptoms; (3) that it appears regularly in a determined period of the general infection; (4) that it has a typical course and duration; and (5) that specific treatment leads to a favorable outcome.

The actual pathogenesis of the jaundice in acute syphilis has been difficult to establish because of the paucity of pathologic material. Warthin⁴⁵ alone has reported the demonstration of *Tr. pallidum* in the liver of a patient in the secondary stage of adult syphilis. Other theories of the mechanism of this jaundice include interstitial inflammation,⁴⁰ hemolytic jaundice,^{2,11} roseola of the bile ducts, portal lymphadenitis obstructing the bile ducts, duodenal catarrh, and syphilitic hepatitis.

The introduction of arsenical therapy has further complicated the question of syphilitic jaundice. The hepatotoxic action of the organic arsenicals has been well demonstrated both in experimental animals and in man, with results ranging from mild degenerative changes to acute yellow atrophy. Wile and Sams⁴⁹ computed an increase of jaundice in early syphilis from 0.18% in untreated patients to 1.37% in those given arsenical therapy. Although some of these instances of jaundice during treatment are clearly manifestations of arsenic toxicity, substantiated by the evidence of Moore²⁴ and Sager,³⁴ others may be syphilitic hepatitis occurring because of insufficient treatment and responding to further antisyphilitic therapy, and still others intercurrent acute catarrhal jaundice. Statistics from large army and navy groups (Soffer,³⁹ Ruge,^{32,33} have shown a striking parallel between the incidence of postarsphenamine jaundice in syphilitic and that of acute catarrhal jaundice (non-specific acute hepatitis) in non-syphilitic men of the same locations.

The mechanisms for the occurrence of jaundice in early syphilis have been variously postulated as:

Untreated (due to syphilis):

- Roseola of bile ducts
- Lymphadenitis compressing bile ducts
- Spirochetosis
- Hyperemia of intrahepatic bile ducts
- Duodenal catarrh
- Hemolytic jaundice
- Syphilitic hepatitis

Treated:

Herxheimer effect
Syphilitic hepatitis with inadequate treatment, hepato-recurrence
Arsenical hepatitis
Bismuth hepatitis
Mercurial hepatitis

Coincidental:

Catarrhal jaundice
Cholelithiasis

The simultaneous occurrence of acute yellow atrophy and syphilis was first recorded in 1836 by Bright.⁴ By 1908 Fischer¹⁰ collected a total of about 50 cases from the literature. Osler²⁸ attributed 10% of all cases of acute yellow atrophy to early syphilis. Since 1914, undoubtedly because of the widespread use of specific treatment, there have been very few cases reported of acute yellow atrophy in untreated syphilis. Survey of the literature to date reveals 59 cases of acute yellow atrophy of the liver in acute syphilis, proven at autopsy, not related to arsenical treatment. Of these, 21 were women, of which at least 2 were pregnant, 15 were men, and the rest not designated. All were between the ages of 2 and 39, most between 16 and 25. Most were in the secondary stage, but 4 occurred during the primary stage of syphilis. In 12 treatment with mercury preparations preceded the onset of jaundice. There have been 2 cases diagnosed as acute yellow atrophy clinically because of decreasing liver size, mental confusion, and the presence of crystals of tyrosine and leucine in the urine, both recovering with specific therapy; Umber's case⁴⁴ treated with arsphenamine, and Wile's⁴⁸ treated with mercury and iodides.

Since the introduction of the arsenicals, there has been considerable increase in the number of cases of acute yellow atrophy associated with early syphilis. By 1930 Bortin³ could collect 90 reported cases of acute yellow atrophy following arsphenamine therapy. McDonagh¹⁹ reported 5 cases of jaundice and 1 of acute yellow atrophy in early syphilis seen in the period from 1906 to 1914; from 1914 to 1918 he saw 21 cases of jaundice and 8 cases of acute yellow atrophy in patients whose acute syphilis was being treated by arsphenamine. Neoarsphenamine has been found to be less toxic than arsphenamine (Schamberg³⁵). The only report of acute yellow atrophy following treatment with mapharsen was that of Zellermyer.⁵⁰

The similarity of syphilitic acute yellow atrophy to that which follows acute catarrhal jaundice has been pointed out by Senator,³⁷ Buschke,⁵ and Herxheimer.¹³

Clinical Picture. Clinically, acute syphilitic hepatitis differs little from acute catarrhal jaundice. Often there is less systemic reaction—less malaise, fever, or gastro-intestinal symptoms—but this is not sufficiently distinctive to be of diagnostic importance. Only the demonstration of the spirochete or the presence of positive serologic tests for syphilis gives presumptive evidence that syphilis is the cause of the jaundice.

Similarly acute yellow atrophy associated with acute syphilis is no different clinically from that of other causes. It usually begins in-

sidiously like a benign hepatitis, often with hepatomegaly. There may or may not be fever, malaise, muscle pains, nausea, vomiting, or pruritis. Then rather suddenly there comes a turn for the worse, marked especially by psychic and neurologic disturbances—headache, restlessness, disorientation, delirium, hyperactive reflexes, convulsions—finally coma and death. During this latter phase the liver becomes rapidly smaller. Crystals of tyrosine and leucine often appear in the urine, and frequently the patient has a striking pungent odor, suggestive of acetamide. Terminally there is usually a little fever.

Case Report. M. H., a 15 year old, single, white school girl, was admitted to the Medical Service of the Vanderbilt University Hospital on October 30, 1942, with the complaints of rash and jaundice. Her illness had begun about 3 weeks before with a small round, red, raised, burning lesion on the left labium, occurring about 3 to 4 weeks following last sexual exposure. The genital lesion subsided spontaneously in 3 or 4 days, but about 2 weeks before admission small, round, red, raised, non-pruritic lesions appeared on the labia, and soon after on the face, hands, arms, legs, and feet. About 10 days before admission the urine became dark. Eight days before admission her skin and eyes became yellow, the jaundice deepening progressively to the time of admission. During the week before admission she had malaise, slight fever, anorexia, and nausea. She had received no treatment.

Physical Examination. On admission her temperature was 101° F., pulse 82, blood pressure 116/80. There was marked icterus of the skin, sclerae, and mucous membranes, but the patient did not appear very ill. There was a widespread papular eruption over the entire skin surface, most profuse on the palms and soles. There was a general glandular enlargement, most marked in the inguinal regions. The tonsils were enlarged and inflamed, with mucous patches. Liver and spleen were not palpable, the liver edge being percussed 3 cm. above the costal margin, with the upper border at the normal level. There was considerable inflammation and edema of the vulva with small ulcers, and a profuse white purulent vaginal discharge. Reflexes were hypoaactive. During her entire stay a peculiar pungent, mousy odor was noticed constantly in her room.

Laboratory Data. Dark-field examination of scrapings from one of the skin lesions revealed *Tr. pallida*. Wassermann and Kahn tests were strongly positive. The urine contained bile. Stool was light in color, but gave a positive test for bile. Icterus index was 45, van den Bergh test positive immediate direct, prothrombin time 29 seconds (less than 20% of normal). A flat Roentgen ray film of the abdomen showed that the liver was apparently normal in size.

Course. On November 2, after the icterus index had risen to 60, the patient was given 0.015 gm. of mapharsen intravenously and 0.13 gm. of bismuth subsalicylate intramuscularly. That evening the temperature rose to 103° F., and all the skin lesions were surrounded by erythema. On the following day the temperature dropped to normal, and the exacerbation of the skin lesions had subsided. Icterus index was still 60, and serum bilirubin was 23.6 mg. per 100 cc. On November 4, without any specific therapy or any complaints, the temperature again rose to 103.6° F. On November 5, mapharsen 0.03 gm., was given intravenously. The temperature rose to 101° F., but there was no change in the skin lesions. On that day the icterus index was 45. On November 6, she received 0.13 gm. of bismuth subsalicylate intramuscularly, with a subsequent rise of temperature to 100.6° F. On November 8, mapharsen 0.04 gm. was given intravenously. By this time she was afebrile, the skin lesions were subsiding, and the ulcers of the vulva were smaller. However, the jaundice persisted unchanged, with the icteric index 60, serum bilirubin 31 mg. per 100 cc., and prothrombin time consistently less than 20% of normal, in spite of daily injections of vitamin K. On the afternoon of November 10,

the patient said that she felt queer and thought she was going to die, but no objective changes were noted. The next day she complained of extreme weakness, and became progressively more confused and disoriented, with nausea and anorexia. By evening she was stuporous. Her neck was not stiff. Her pupils were widely dilated, but reacted to light. Eye-grounds were negative. The liver edge was questionably palpable in the midepigastrium, but liver dullness was still very small. Reflexes were equal and active. Lumbar puncture revealed clear yellow fluid under pressure of 145 mm. of water, containing no cells. Spinal fluid protein and sugar were normal, and Wassermann test was negative. No tyrosine or leucine crystals were demonstrated in the urine. Icterus index was 60 and remained so until death. On November 12 she was extremely lethargic, and on November 13 it was noted that the left arm was flaccid with very hypoaactive reflexes, although all the other tendon jerks were hyperactive. Kernig's sign was negative. There was a positive Babinski reflex bilaterally. On November 15, a sustained clonus was noted in both ankles, and temperature went up to 101.4° F. The following day respirations became labored and stertorous, and many coarse râles were heard throughout the chest. Her temperature was 102.8° F., and leukocyte count 20,000. Sulfathiazole was given by gavage. Lumbar puncture revealed clear yellow fluid under markedly increased pressure, containing 176 red blood cells and 13 white blood cells per c.mm. During this last week she was treated with parenteral glucose and saline, transfusions of fresh whole blood, and oxygen. On the morning of November 17 she developed some muscular twitchings of her face and deep gasping respirations, and died in about half an hour.

PATHOLOGIC REPORT (limited to positive findings): The patient was seen to be deeply jaundiced with the remnants of a generalized red-brown maculopapular eruption involving the scalp, face, extremities, and vulva. The *peritoneal cavity* contained 50 cc. of dark yellow-green fluid. The fat was dark yellow in color, and contained numerous petechial hemorrhages. The peritoneal surfaces were stained yellow and were smooth, shiny, transparent, and glistening. The mesenteric and retroperitoneal *lymph nodes* were enlarged and soft. The posterior portions of both *lungs* were firm and resistant. The epithelial linings of the *bronchi* were hemorrhagic, and there was a small amount of brown frothy fluid in the bronchial lumina. The hilar and mediastinal nodes were enlarged, yellow, and soft. Posterior to the second portion of the duodenum was a small retroperitoneal hemorrhage. The *gastric rugæ* were unduly prominent and hemorrhagic, with moderate edema, but no areas of ulceration. The *liver* weighed 1000 gm., had thin, well-demarcated edges and a smooth, shiny capsule without evidence of wrinkling. It was a bright red color with several small, elevated, yellow nodules on the anterior and posterior surfaces of the right lobe. The liver was of a firmer consistency than normal except for the yellow nodules, which felt like normal liver tissue. The red areas were firm, contained excess fibrous tissue, and did not show the normal liver lobules. The yellow areas contained distorted lobulations. The *gall bladder* was small and contracted, slightly thickened, but with normal, patent ducts, no stones. The *spleen* weighed 280 gm. and showed prominent Malpighian corpuscles and a generally hyperplastic appearance. The *kidneys* were enlarged and soft, with normal shape and contour. The *brain* was slightly softer than usual and generally edematous, but there were no areas of hemorrhage or softening.

MICROSCOPICALLY the *liver* parenchyma appeared disintegrated and necrotic. The remaining liver cells were irregular, distorted, granular, and arranged in cords. Many showed extremely dark nuclei and many clear zones. The remainder of the liver substance was represented by cellular débris, massively infiltrated by small round cells, polymorphonuclear leukocytes, large mononuclear leukocytes, and macrophages. These necrotic areas contained albuminous granules, fat globules, masses of bile pigment. The sinusoids were widely distended, and small foci of hemorrhage were evident. This destruction was generalized, but appeared to be most marked about the central veins. The

vessels were engorged, and their walls showed a small round cell and macrophage infiltration. There was a rather marked bile duct proliferation, about which there was an infiltration by lymphocytes and plasma cells. Scattered throughout all sections there were patchy areas in which there appeared to be a fibroblastic proliferation. The large bile ducts were lined with extremely tall columnar epithelium. The capillary tufts of the *kidneys* were engorged with blood, and many showed hemorrhage on the basement membrane. A few appeared abnormally cellular, due to the presence of macrophages within the tuft. The tubules showed marked cloudy swelling. The *meninges* were thickened and moderately infiltrated by lymphocytes, large mononuclears, and macrophages. The subpial space contained an amorphous pink precipitate. The cellular infiltration accompanied the meninges into the brain substance. The meningeal vessels were markedly engorged with extravasation in many regions. The cortical neurons showed a normal distribution with no significant changes. The perivascular spaces were wider than normal, with occasional small hemorrhages.

The ANATOMIC DIAGNOSES were acute yellow atrophy of the liver, secondary syphilis, acute bronchopneumonia, focal glomerulonephritis, acute uterine cervicitis, cerebral edema and congestion, acute splenic tumor.

Discussion. This patient, then, was a 15 year old girl, who developed jaundice shortly after a secondary syphilitic eruption, and who progressed to acute yellow atrophy of the liver, dying about a month after the onset of jaundice. At the time of admission her liver was small to percussion and apparently about normal size by Roentgen ray—not enlarged as one might expect in a simple syphilitic hepatitis. Acute yellow atrophy was considered at that time, but its extreme rarity and the apparent normal liver contour by Roentgen ray favored the diagnosis of syphilitic hepatitis. Consequently specific therapy was decided upon. The patient developed a typical Herxheimer phenomenon (fever and exacerbation of skin lesions) after the first injection of mapharsen and bismuth, and a much milder one after the second mapharsen injection. The skin lesions began clearing satisfactorily. However, the failure of the jaundice to improve cast some doubt on its syphilitic etiology and suggested an intercurrent acute catarrhal jaundice. About this time the patient became suddenly worse, with stupor, hyperactive reflexes, clonus, positive Babinski reflex, dilated pupils. The predominance of neurologic symptoms with negligible fever or gastro-intestinal symptoms and the onset 3 days after the last injection suggested hemorrhagic encephalitis caused by mapharsen, or a cerebral hemorrhage related to the prothrombin deficiency. However, the autopsy showed typical acute yellow atrophy of the liver, with only cerebral edema, no hemorrhagic lesions in the brain.

The question arises as to the nature of this patient's liver disease. Did she have syphilitic hepatitis resulting in acute yellow atrophy because of the added hepatotoxic effect of mapharsen? Did she have acute yellow atrophy from the onset? Did she have acute catarrhal jaundice? Would she have recovered on heavy metal therapy, or on more vigorous arsenical therapy? These questions cannot be answered with our present knowledge. We doubt that her death was due solely to arsenic, since of her three doses only the last was of therapeutic size. The occurrence of the jaundice almost simultaneously with the secondary syphilitic eruption strongly suggests that it was syphilitic in

origin. If the jaundice was due to syphilitic hepatitis, we believe that it was probably a grave form from the onset and progressed to acute yellow atrophy in spite of treatment. The other possibility, an acute infectious hepatitis, cannot be ruled out.

From an extensive search of the literature there have been collected 31 cases of syphilitic hepatitis with jaundice, in which arsenical therapy brought about rapid clearing of the jaundice. *Not a single instance has been found in which the use of arsenic in the presence of jaundice resulted in acute yellow atrophy.* Thus, our case is unique. This patient had secondary syphilis and jaundice, was given mapharsen and bismuth, and subsequently died of acute yellow atrophy of the liver.

TABLE 1.—SYPHILITIC HEPATITIS TREATED BY ARSENICAL PREPARATIONS

Author	Sex	Age	Stage	Treatment before jaundice	Diagnostic proof	Treatment after jaundice
Dubot ⁸	M	49	1	Hebetin	DF	Arsphenamine
Umbert ¹	F	19	2	"Mixed treatment"	W	Arsphenamine
Milian ²²	F	..	2	Neoarsphenamine	..	Neoarsphenamine
Scott & Pearson ³⁶	M	21	2	Neoarsphenamine and mercury
	M	21	Neoarsphenamine and mercury
Milian ²²	F	21	2	DF	Neoarsphenamine and mercury
	M	38	2†	Olarsol and neoarsphenamine	..	Neoarsphenamine and mercury
Chatellier ⁶	F	22	1, 2	DF, W	Neoarsphenamine
Benesch & Crehange ¹	F	21	1, 2	Arsenical
Nicaud ²³	F	32	1, 2	DF	Neoarsphenamine
Nicaud ²⁶	F	23	1, 2	W	Arsphenamine and mercury
Tobias ¹²	F	20	2	DF, W	Arsphenamine
Mattes ²¹	6 or 7 cases	Arsphenamine
Tzanek ⁴³	2	Arsenical (3 doses)	..	Arsenical
	2	Neoarsphenamine	W	Arsenical
Wangh ⁴⁶	F	25	2	Kl, Ka	Neoarsphenamine
	M	22	1, 2	Kl, Ka	Neoarsphenamine and bismuth
Creswell ⁷	M	19	2	W, Ka	Bismuth and arsenoxide
	M	26	1	W, E	..
Lane ¹⁷	M	29	2	Arsphenamine and bismuth
Moore ²¹	3 or 4 cases	Arsenical
Rattner ²⁰	M	33	2	DF, W	Neoarsphenamine
Kampmeier ¹⁵	M	..	2†	W	Neoarsphenamine
Kampmeier ¹⁶	M	30	2†	DF, W, Ka	Neoarsphenamine

† Relapse.

1, primary; 2, secondary; DF, dark-field; W, Wassermann; Ka, Kahn; Kl, Kline; E, Eagle.

The accompanying table summarizes the reported cases of patients with syphilitic hepatitis, who were treated with one of the arsphenamines. It was interesting to compare these results with those obtained by treatment with mercury, iodides, and bismuth. Heavy metals alone brought about clearing of the jaundice in most cases, but after an average of 1 or 2 months instead of 1 to 3 weeks. One may question whether some of the patients who died of syphilitic acute yellow atrophy in spite of treatment with mercury or bismuth might have been saved by arsenical therapy. Since improvement with heavy metal treatment was very slow, it is reasonable to doubt whether it had any appreciable effect on the syphilitic hepatitis, or whether the jaundice in those cases cleared spontaneously.

This brings up the still debated question of the best way to treat patients with jaundice in acute syphilis. Because of the occurrence

of jaundice after arsenical treatment and the experimental evidence of the toxicity of arsenic for the liver, there has been prejudice against the use of arsenical therapy especially at the onset of treatment. Scott and Pearson³⁶ advocated preliminary treatment with mercury and iodides for several weeks to months, then cautious use of an arsphenamine. Wile,⁴⁷ although admitting the brilliant results sometimes achieved with arsenical therapy, recommended that it not be used as a routine measure in hepatic syphilis. Elliott and Todd,⁹ Smith,³⁸ and MacDonald²⁰ believed that arsphenamines were contraindicated. O'Leary²⁷ advised the prolonged use of preparations of mercury and iodides preliminary to the use of arsphenamine. Stokes,⁴¹ in benign hepatitis, recommended bismuth until the icterus index returned to normal, then arsphenamine in moderate doses. For grave icterus he felt the vigorous use of bismuth the best treatment.

On the other hand, Umber⁴⁴ reported a case of jaundice in acute syphilis, diagnosed acute yellow atrophy because of the rapid decrease in size of the liver and the presence of leucine and tyrosine crystals in the urine, which responded well to arsphenamine, making a rapid recovery. He advised that in acute yellow atrophy with a positive Wassermann test one should not delay arsphenamine therapy. Langevin and Brule¹⁸ considered the hepatotoxic action of arsphenamine negligible compared with its therapeutic activity. Mattes,²¹ in discussing Smith's paper, cited 6 or 7 cases treated with arsphenamine, recovering without complications. Rolleston³¹ recommended that the treatment be that of the syphilis, not that of jaundice. Irgang and Sala¹⁴ believed that the presence of a mild syphilitic hepatitis was no contraindication to arsphenamine therapy. Waugh⁴⁶ reported good results from the use of arsphenamine. In early syphilitic hepatitis, Moore²⁴ advised the use of arsphenamine as in uncomplicated early syphilis, starting with smaller doses, but working up quickly to the usual therapeutic dose. In all his (3 or 4) observed cases the jaundice rapidly cleared, there were no evidences of decreased tolerance for the arsenicals, and the patient's subsequent progress was uneventful. As to acute yellow atrophy in early syphilis, he reported that it "is so rare that we have never seen a case. Reported instances have been so rapidly progressive and the prognosis so grave that therapeutic efforts can not be limited to the slower acting heavy metals. Neoarsphenamine or mapharsen should be employed."

No one person sees enough of such patients to be able to accumulate an adequately controlled series. In view of the incompleteness of clinical evidence of deleterious effect of arsenical therapy in the jaundice of early syphilis, and the reports of prompt relief of symptoms by specific therapy, we believe that the published weight of evidence is in favor of its use. We must bear in mind, however, the general tendency not to report unfavorable cases. Many patients have been cured of their jaundice by mercury, iodides, or bismuth, or even without treatment. However, some of these patients die of acute yellow atrophy, whereas the case here reported is the only one known in which arsenical treatment of early syphilitic jaundice has been followed by

acute necrosis of the liver. And it remains to be shown which causes the more permanent liver damage and loss of liver function, the rapidly acting, more toxic arsphenamine, or a more prolonged course of syphilitic hepatitis.

Confronted with this identical situation again, we still would not be sure of the correct answer as to therapy. In spite of the fatal outcome of this patient, we believe that the evidence gathered from the literature justifies the use of arsenical treatment in acute syphilitic hepatitis. We are of the opinion that vigorous treatment with one of the arsenical preparations and bismuth, together with the usual supportive measures in liver disease—high carbohydrate, high protein, low fat diet, adequate fluids, high vitamin intake, transfusions—offer the best chance for success.

Conclusions. 1. An unusual case of acute yellow atrophy in secondary syphilis with death after 3 injections of mapharsen and 2 of bismuth is reported.

2. The literature concerning jaundice in acute syphilis, its pathogenesis and treatment, has been briefly summarized.

3. Syphilitic hepatitis responded favorably to arsenical treatment in all the 31 reported cases.

4. Although knowledge of the subject is incomplete, and although our patient died of acute yellow atrophy after a small amount of mapharsen therapy, we believe that until the cases with bad effects have been adequately reported, we can only say at present that the literature supports the stand that the use of the arsphenamines in the treatment of jaundice in acute syphilis is justified.

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OBSTRUCTION OF THE HEPATIC VEINS (CHIARI'S DISEASE)

REPORT OF FIVE CASES

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IN this paper we are reporting 5 cases of a rare disease, hepatic vein thrombosis. This condition was described by Budd⁴ as early as 1846, and endophlebitis of these veins was recognized as a pathologic entity by Chiari⁷ in 1899. The clinical aspects were defined by Hess¹² in 1905 and by Thompson and Turnbull²⁵ in 1912. Two instances of neoplasm obstructing the hepatic veins were reported in the next decade,^{15,27} and Hoover¹³ in 1920 found 30 cases in the literature. A tabular synopsis of cases reported since 1920 is given in Table 1.

A variety of etiologic factors has been reported for hepatic vein obstruction. They include primary thrombosis and thrombophlebitis;^{4,12} primary endophlebitis;⁷ local and general infection;^{6,23} stasis;² systemic disease, in most cases polycythemia vera;^{1,2,3,8,19,21,24,26} and mechanical obstruction by anomaly^{7,12} or neoplasm.^{14,15,27} Early writers favored alcoholism,⁴ syphilis⁷ and mechanical stresses asso-

ciated with pregnancy²⁵ or chronic cough¹² as causative agents, but these must be exceedingly rare. Only one definitely positive Wassermann reaction appeared in one series of 8 cases.⁵

Thrombosis occurs most frequently where the hepatic veins empty into the inferior vena cava, perhaps because of eddy currents formed at the oblique entering angle.^{2,13,15} As thrombosis of the hepatic veins is often accompanied by inflammatory changes in the inferior vena cava,^{3,22} it is probable that the two processes are often continuous, proximity and eddy currents aiding in the spread of infection from one vein to the other. Hepatic vein thrombosis may be partial or complete,¹³ or complete with recanalization.^{2,14,19} Collateral circulation is common when the obstruction occurs gradually,²⁵ and the ratio of collateral circulation to circulation lost by obstruction determines the symptoms experienced by the patient.¹⁴ Postmortem examinations show a characteristic central necrosis of the liver lobules, congestion of blood in this locality, replacement fibrosis of the liver, and enlargement of the spleen.¹⁴ Enlargement of the liver is due to engorgement, the organ being actually smaller than normal when the blood has been removed.¹

Hepatic vein obstruction appears with equal frequency in men and women ranging in age from 17 months (cited¹²) to 70 years.¹⁶ Most cases (over 50% in Table 1) occur between the ages of 20 and 40 years.^{9,12,16} The disease may appear in the acute or the chronic form.¹² The acute form^{1,2,3,6,9,21} is sudden in onset with obscure abdominal pain, nausea, vomiting, abdominal guarding and shock,⁹ followed by ascites, tenderness and enlargement of the liver and spleen, delirium, coma and death in 1 to 4 weeks. The chronic form is gradual in onset, with indigestion, epigastric pain, ascites and tender enlargement of the liver, collateral circulation, cyanosis, rarely jaundice; with eventual coma, delirium and death—often within 6 months, sometimes after several years.^{10,14,22,23,24} Cases with prolonged survival reported without autopsy¹³ are open to question, although life is possible in the presence of limited thrombosis of the hepatic vein with incomplete occlusion of the vein, early recanalization, or the development of adequate collateral circulation. Symptoms may not appear until hepatic vein occlusion is almost complete.¹³

Pain over the liver, sometimes radiating to the back and shoulders, rapid accumulation of ascites resistant to diuretics, simultaneous enlargement of a smooth-edged liver and spleen, development of a collateral circulation and edema of the legs suggest hepatic vein obstruction. There may be signs of associated disease, notably infection or polycythemia vera, of which hepatic vein thrombosis may be considered a severe complication.²⁴ In several cases ascites has been associated with pleural fluid.^{1,13,19}

Jaundice and bilirubinuria are infrequent.¹³ There may be a lowered plasma cholesterol with absent ester fraction,^{1,24} and an elevated blood urea.¹

The terminal episode is usually coma occasioned by hepatic insufficiency, although there may be oliguria and acidosis¹⁵ and a state

TABLE 1.—TABULAR SYNOPSIS OF CASES OF CHAIK'S DISEASE REPORTED SINCE 1920

Reported by	Age	Sex	Duration	Type of death	Symptoms and signs	Ascitic fluid	RBC (mill.)	Hb. (%)	WBC (thous.)	Other laboratory data	Findings in hepatic veins at autopsy
Hoover ¹¹	?	M	..	Lived	Abd. pain, liver enl., ascites, pleural eff.	Opalescent, 1,014 (27 abd. taps, oec. WBC	4.8	65	1.2	Nor. bile formation and excretion ? Wass.	
Hoover ¹¹	31	M	..	Lived	Ascites, liver enl., pl. effusion	Clear yellow, 1,008, 600 cells (? type)	360,000 platelets	Platelet thrombus
Oppenheimer ²¹	19	F	3 wks.	..	Ascites, liver enl., spleen enl.	8.83	124	3.4	Recanalized thrombus
Baehr and Klempner ²	49	F	3 wks.	Postop. collapse	Abd. pain, liver enl., spleen enl., jaundice	6.0	110	9.9	Wass. neg.	Occlusion, anast. with veins of diaphragm
Hutchinson and Simpson ¹	28	M	? 25 yrs. or 1 mo.	Postop. collapse	No ascites	Wass. neg.	Thrombosis
Cole ³	33	M	4 mos.	Coma	Liver enl., spleen enl., ascites	23 abd. taps removing 147 liters	8.6	120	17.1	Wass. neg.	Phlebitis of hepatic and portal veins and inf. vena cava
Rigdon ²²	22	F	Recurrent	Hemorrhage	Recurrent ascites for 2½ yrs.	Clear yellow, 1,013, protein 1.19 mg. per 100 cc., cholesterol 65 mg. per 100 cc.	4.56	94	10.1	Wass. neg., BMR -22%	
East ¹⁰	38	M	..	Lived	Liver and spleen enl., ankle edema, collat. circ.	4.9	102	11.6	Old lues	Thrombosis
Ciambrier and Dagnelies ³	51	M	2 wks.	..	Signs of generalized infection	Wass. neg.	Antemortem clot
Savin ²³	27	M	2 mos.	..	Liver enl., ascites, collat. circ.	Wass. neg., PCV 60%, H+22,	Thrombosis
Solva ²⁴	80	M	2 mos.	Postop. (ompho- topexy)	Liver enl., ascites, jaundice, pleural eff.	Bile stained	7.43	110	27.5	220,000 platelets	Old thrombosis
Ulhorn ²⁵	38	F	Spleen enl., jaundice	8.7	110	49.7	Wass. neg.	
Berk ³	56	F	1 mo.	..	Abd. pain, liver enl., spleen enl., ascites, jaundice	7.2	115	12.0	
Norman and Allen ¹⁰	54	F	Spleen enl., ascites	Recanalized thrombosis
McAlpin and Smith ¹⁹	57	F	Liver enl., ascites, jaundice	6.8	125	8.3	Recent and old thrombosis
Altshule and White ¹	27	M	4 wks.	Coma	Spleen enl., ascites, pl. effusion, jaundice	Clear yellow, 800 cc., 1,016, 2.8 mg. per 100 cc, protein	6.7-6.9	121-132	11.0-21.0	Thrombosis
M.G.H. Case 27431 ¹⁷	62	M	3 wks.	Coma	Abd. pain, jaundice, signs of infection	4.0	60	18.4	van den Bergh biphasic	Thrombosis (with cholangitis and abscess)
Kahn and Sprague ¹⁶	21	F	1 mo.	Coma	Abd. pain, spleen enl., nausea	4.1	78	14.2	Alb., blood sugar 118.4 mg. per 100 cc.	No postmortem
Dickinson ⁸	26	M	2½ days	Postop.	Abd. pain, liver enl., spleen enl., ascites, vomiting, diarrhea	Clear straw-colored, 2500 cc.	16.1	Wass. neg.	Acute complete thrombophlebitis
M.G.H. Case 29192 ¹⁸	42	M	Ascites	66	6.7	40% BSP retent., 26 sec., prothr. time, 1+ cephalin-cholesterol flocculation	Thrombophlebitis

approximating the so-called hepatorenal syndrome.^{16,23} Sudden swelling of the liver and onset of acidosis, when superimposed upon signs of inferior vena cava obstruction, probably indicate occlusion of the hepatic veins.¹⁵

Hepatic vein obstruction is rarely diagnosed during life, as the clinical picture is that of portal vein obstruction and hepatic insufficiency. Liver enlargement, jaundice and ascites are, however, more marked in hepatic than in portal vein obstruction;²⁴ collateral circulation tends to flow caudad in hepatic vein obstruction and cephalad in inferior vena cava obstruction;²⁵ and the smooth, tender liver and more rapid formation of ascites distinguish hepatic vein obstruction from cirrhosis. In its acute form, Chiari's disease may be mistaken for a surgical emergency,⁹ and the chronic form has been closely simulated by primary tumor of the inferior vena cava without hepatic vein involvement.¹¹

No method of treatment has been suggested; patients have died shortly after attempts at omentopexy^{24,25} and after other operations.^{9,14,16,21}

Almost 60 instances of this disease have now appeared in the literature, but the cases are still isolated, and more frequent reports may be expected to follow more careful routine postmortem examination of the hepatic veins.^{5,12} Only 5 instances of hepatic vein thrombosis have been found among the 11,979 autopsies done by members of the Stanford Department of Pathology since 1898, an incidence of 0.042%. These 5 cases are described below; the most recent, about which more details are available, is set forth at greater length.

Case Reports. CASE 1. J. H., a 28 year old Mexican, entered the hospital on October 27, 1926, after 5 days of fever, cough, pleurisy, abdominal pain and constipation. The pain in the abdomen had begun gradually in the epigastrium and right upper quadrant and the abdomen had rapidly enlarged.

Physical examination showed a blood pressure of 92/66, the pulse was 100 to 140 per minute, and the respirations 28 to 35 per minute. There was a bilateral bronchopneumonia. The abdomen was greatly enlarged and tender in the right upper quadrant and there was marked enlargement of the liver. The red blood cells numbered 4.8 million with 85% hemoglobin and 15,000 white blood cells (83% neutrophils). The urine contained many hyaline casts. The Wassermann test was negative. The spinal fluid was under normal pressure and gave a negative Pandy reaction.

The patient died 4 days after entry.

Postmortem examination (30-46) revealed 250 cc. of slightly turbid dark yellow fluid in the abdomen. The liver was enlarged and adherent to the diaphragm, beneath which lay an abscess filled with thick creamy pus and 1.5 cm. in diameter. Fibrous tissue connected this abscess with a second abscess which lay within the substance of the liver and measured 4 cm. in diameter. There were recent thrombi in many small and several large hepatic veins. Histologic examination showed the liver to be hyperemic and edematous. Cultures taken from the abscesses grew Hiss-Russell dysentery bacilli, *B. coli*, and non-hemolytic streptococci. No amebæ were found.

CASE 2.—F. R., a 56 year old white male, entered the hospital November 20, 1934, because of an epigastric mass of 1 month's duration. A duodenal ulcer has been diagnosed by Roentgen ray in 1926 and the patient had obtained some relief with diet.

Physical examination showed an emaciated man with an easily palpable irregular epigastric mass. The lymph nodes were not enlarged.

The blood and urine were not remarkable in 1933 but the hemoglobin fell to 51% in December, 1934, and 30% in February, 1935, when the serum proteins were 4.2 gm. per 100 cc. (albumin 2.6 gm., globulin 1.6 gm.). The patient became progressively weaker, developed edema of the extremities and died on March 1, 1935.

Postmortem examination (38-245) showed a scaphoid abdomen which contained 1000 cc. of slightly turbid blood-tinged fluid. An extensive, ulcerated carcinoma encircled the pylorus of the stomach and extended into the pancreas, omentum, adrenals and liver. The left main branch of the hepatic vein contained a laminated antemortem thrombus.

CASE 3. F. G., a 55 year old Chilean male, entered the hospital on April 25, 1936. The patient had for years taken daily a quart of wine; in 1906 he had noted a penile sore. In 1928 he vomited 500 cc. of blood, and in 1932 his abdomen became distended and he required a number of paracenteses. Physical examination in 1932 showed a blood pressure of 112/70. There were telangiectases on the nose; the pupils were slightly irregular. The heart and lungs were not remarkable but the abdomen was distended and presented a fluid wave. Liver dullness extended 5 cm. below the right costal margin, and a firm smooth spleen was palpable 3 cm. below the left costal margin. There were a few dilated veins on the abdomen. Four thousand cc. of yellow fluid were withdrawn.

The white blood cell count ranged from 2100 to 7000 with a 48% lymphocytosis. The urine was negative. A blood Wassermann was positive in 1932 and 1934. The spinal fluid was Wassermann-negative with a Lange curve of 1112211000. The Takata-Ara test was negative.

The patient was given liver, insulin and antilutetic treatment. After May, 1935, his ascites seemed to respond to mercurial diuretics, and he remained in fair health in spite of small hematemeses until April, 1936, when he suddenly vomited 1500 cc. of blood. He was admitted to the hospital *in extremis*, the spleen was palpable 3 cm. below the left costal margin and there was shifting dullness in the flanks. The patient died 2 days later.

Postmortem examination (39-426) showed no free fluid in the peritoneal cavity. The liver was small. The spleen was large and covered with adhesions. Large collateral veins (considered at the time to be congenital malformations) passed from the spleen to the left kidney, abdominal wall, and diaphragm. The esophagus contained large varicose veins, several of which were perforated. The portal vein was filled with organizing thrombus and the right and left hepatic veins were thrombosed, the thrombi containing one or two small vessels. More peripherally, thrombi extended into the splenic, gastric and superior and inferior mesenteric veins and could be followed out to the smallest omental veins. The liver was not remarkable histologically.

CASE 4. H. D., a 34 year old white male, entered the hospital on October 15, 1938, after 1 month of weakness, malaise and throbbing pain in the left upper quadrant. An operation 6 days later disclosed a hypernephroma on the left with extension of tumor into the left renal vein. The kidney was removed and the patient left the hospital in 3 weeks, feeling well except for moderate chest pain and wheezing. Chest and bone Roentgen rays, taken at intervals, were negative until October, 1939, when there were small nodular metastases in both lungs. These did not respond to irradiation. In February, 1940, the liver was enlarged, and 1 month later fluid was present in the chest and abdomen. The superficial abdominal veins were prominent. The patient became icteric, failed rapidly and died on April 20, 1940.

Postmortem examination (OD-177) showed 1000 cc. of slightly bloody, semi-gelatinous fluid in the abdomen. The liver was large and contained 2 large tumor nodules. The entire inferior vena cava from the level of the renal veins to the right auricle was filled with soft, pale yellow to green, friable tumor. All of the branches of the hepatic vein close to and entering the inferior vena cava contained tumor, and on section even the smallest branches were thrombosed.

Histologic examination of the liver showed that the central vein and the sinuses of the central two-thirds of almost all the lobules were filled with blood and the liver cells in this area were atrophic or dead. The radicals of the hepatic vein were filled with organizing thrombus; fibroblasts were growing in from the periphery.

CASE 5.—Mrs. M. McD., a 40 year-old English housewife, entered the hospital on February 15, 1937, after several years of low back pain, abdominal pain and dysuria. The patient had borne 2 living children, had once aborted spontaneously and thrice herself induced abortions. There was no history of alcoholism, and the family and past history were unimportant save for the fact that a positive Wassermann had been discovered in 1930 when her husband had a penile chancre. The patient received about 7 intramuscular injections over a 3 month period, then failed to return for treatment.

TABLE 2.—LABORATORY DATA (Mrs. McD.) FROM 1937 TO 1942

Date	RBC (mill.)	Hb. (%) (S)	WBC (thous.)	Differential				Packed cell vol. (%)	MCV MCHC MCHbC
				Neutr. (%)	Lys. (%)	Monos. (%)	Plate- lets (thous.)		
2-15-37	5.7	86	12.6	68	26	3			
8-14-40	5.6	96	14.7	87	11	2			
8-17-40	9.7	74	24	1			
7- 5-42	5.3	110	18.4	88	7	5			
7- 6-42	5.1	100	16.8	230		
7- 7-42	6.2	94*	22.6	81	16	2	309	53	85.5 25.8 30.2
7-11-42	5.2	106	24.2						
7-13-42	5.2	103	32.1	86	6	1			
7-16-42	6.0	102†	29.3	85	7	4	361	58	96.2 28.7 29.8
7-22-42	5.4	101	29.0	82	14	3			

* 16 gm.

† 17.3 gm.

Explanatory notes: MCV—Mean Corpuscular Volume in cu. micra (normal 80-94). MCHC—Mean Corpuscular Hemoglobin Concentration in micromicrograms (normal 27-32). MCHbC—Mean Corpuscular Hemoglobin Content in per cent (normal 33-38).

Physical examination revealed only relaxation of the pelvic floor, old lacerations of the cervix, and chronic cervicitis. The blood pressure was 120/90; no organs or masses were palpable in the abdomen. The blood and urine were normal; the blood Wassermann was strongly positive. Cervical smears showed no gonococci.

A trachelorrhaphy and perineorrhaphy were done; the patient recovered and she was discharged, failing to return to the syphilis clinic as directed.

The abdomen was not found to be remarkable in August, 1940, when the patient entered the hospital for treatment of pelvic inflammatory disease. On this entry, the blood Wassermann was negative, although the patient remembered only 1 or 2 intravenous injections since 1937. On August 21, 1940, a lumbar puncture yielded a clear colorless fluid without cells. The total protein was 33.4 mg. per 100 cc., and there was a strongly positive Wassermann reaction with 0.1 cc. of spinal fluid. The colloidal gold curve was 5555421100.

On May 12, 1941, there was no clinical evidence of syphilis; but now the blood pressure was 160/90. The liver descended 1 cm., and the spleen 3 cm. below the costal margin. During the following period from May 25, 1941,

until June 19, 1943, the patient received irregular treatments consisting of 26 injections of a bismuth compound, 12 injections of Mapharsen, and 3 of silver arsphenamine. Following these injections she occasionally had chills and fever and jaundice without other signs of toxicity.

The patient entered the hospital for the last time on July 5, 1943. In the preceding 2 months she had had 3 spells of indigestion lasting about a week. She had not vomited or been icteric but had passed a tarry stool 1 week before entry. Five days before entry she noticed a swelling of her abdomen and 2 days later the onset of constant upper abdominal pain, perhaps associated with a darker color of the urine. There had been no change in weight.

Physical examination showed a flushed, sick-looking, slightly icteric woman. There were no spider angiomas. The heart and lungs were not remarkable; the blood pressure was 150/110. The abdomen was tense and protuberant with a definite fluid wave. The liver was tender, smooth and firm and descended 1 cm. below the costal margin; the spleen 4 cm. The surface veins of the lower abdomen were full, but no collateral circulation had been established.

The blood counts upon this and the previous entries are entered in Table 2. The urine, stool and Wassermann examinations were not abnormal. A van den Bergh test was positive in the direct phase with an indirect value of 2.2 units. The icterus index was 17. The sedimentation rate was 18 mm. in 1 hour (Wintrobe), and the packed cell volume was 53%. The serum protein (Kagan) was 6.1 gm. per 100 cc.; the bleeding and coagulation time and the prothrombin time were normal. A bromsulphalein test showed 100% retention in 5 minutes and 80% retention in 45 minutes. After injection of Congo red, 60% of the dye was recovered from the plasma in 30 minutes, 71% in 1 hour.

A chest film showed elevated diaphragm on both sides and an old interlobar pleurisy on the right; the heart shadow was not remarkable. A barium meal revealed a normal esophagus, stomach and duodenal cap.

The gastric contents were normal in volume and acidity. The spinal fluid contained 6 lymphocytes, 23.8 mg. of protein per 100 cc. showed a 5555321000 colloidal gold curve and a positive Wassermann reaction with 0.5 cc. of spinal fluid. Electrocardiograms demonstrated a left axis deviation, a small T_2 and an inverted T_3 .

On the 5th and 14th hospital days 2200 cc. and 4400 cc. of yellow-orange ascitic fluid were removed. The specific gravity of this fluid was 1.010, cultures were negative, and the sediment contained a few lymphoid and polymorphonuclear cells in equal proportions.

Careful study of a blood film showed 0.4% reticulocytes, some variation in the size and shape of the red blood cells, and an occasional normoblast and myelocyte with a shift toward nuclear immaturity. Sternal marrow puncture material showed (Dr. H. A. Wyckoff): "Normoblasts and megaloblasts of the pronormoblastic type . . . relatively increased in numbers. . . . myeloblastic cells—somewhat more than usually numerous. These relationships together with rather more than usually numerous mitotic figures suggest hyperplasia of the marrow with especially active multiplication of erythroblastic cells of the normal series type."

On the 20th hospital day the patient complained of weakness; 2 days later she became much weaker and more listless, a blood sugar was 108.7 mg. per 100 cc. Four hours later her respiration became slow and difficult, her pulse slow and full. She was covered with perspiration, became delirious, then comatose, and died in spite of supportive measures.

Postmortem examination (2D-216) showed a distended abdomen containing 2200 cc. of clear yellow fluid. The liver extended 3 cm. below the costal margin. The peritoneal surfaces were smooth and glistening, but the gall bladder, pelvic organs and spleen were involved by adhesions. These adhesions and the peritoneal surfaces were extremely vascular.

The thoracic cavity contained no appreciable free fluid. There were collections of inflammatory cells in the myocardium suggestive of an acute localized

myocarditis. There was edema of the lungs which contained many recently infarcted areas. No esophageal varices were found.

Histologic examination of the spleen and liver showed numerous scattered small islands of hematopoiesis. Sections of the main hepatic veins near their emergence into the vena cava showed an almost complete obliteration by organizing thrombi with some degree of recanalization at their margins. The vein walls were not abnormal and contained no preëxisting intimal plaques. There was a slight lymphocytic infiltration of the walls and an increased vascularity of the adventitia. Other hepatic veins deeper in the liver were occluded by old partially recanalized thrombi and throughout the liver most of the lobules showed necrosis of the central liver cells and dilatation of the central liver sinusoids. A section of the intrahepatic portion of the inferior vena cava was not remarkable except for a small intimal plaque which appeared to be an advanced stage in the organization of a thrombus. Similar plaques were found in the portal and splenic veins and even in a small vein of the pancreas.

No syphilitic lesions were found, even in the central nervous system.

Discussion. These cases illustrate several clinical and pathologic types of hepatic vein thrombosis. In Case 1, infection was a predisposing factor. In Case 2, the thrombosis was associated with metastatic gastric carcinoma, and in Case 4 with the typical dissemination of hypernephroma along the inferior vena cava. In Cases 1, 2 and 4 thrombosis was unimportant as a cause of death and probably occurred just before the patient expired.

Cases 3 and 5 had hepatic vein thrombi which showed recanalization, and each patient had established some collateral circulation. In Case 3 thrombosis may have occurred 4 years before death, yet the restoration of blood flow was such that the patient survived to die of esophageal hemorrhage.

Case 5 developed thrombi in the portal and hepatic venous systems over an unknown length of time. The enlarged liver and spleen 14 months before the final episode, and the indigestion, ascites and abdominal pain 4 months before death presumably indicate episodes of hepatic vein thrombosis. These thrombi eventually led to hepatic insufficiency. No esophageal varices developed although the passive hyperemia of the liver was extreme.

Long-standing and inadequately treated syphilis seemed to have no etiologic significance in Cases 3 and 5.

Only Case 5 exhibited polycythemia; and, although in this patient the red blood counts were slightly elevated for several years, the bone marrow was hyperplastic and there was extramedullary hematopoiesis in the liver and spleen. Still the evidence for polycythemia vera is much less striking than in the majority of cases with both polycythemia and hepatic vein thrombosis.

Summary. Five cases of obstruction of the hepatic veins (Chiari's disease) are reported with autopsy findings. The literature is reviewed and cases of this condition reported since 1920 are gathered in a tabular synopsis. The diagnosis is rarely made during life. It should be considered in any patient with progressive tender enlargement of the liver and spleen accompanied by ascites and abdominal pain.

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MENINGOCOCCAL INFECTION

I. MENINGOCOCCAL MENINGITIS AND SEPTICEMIA

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SIGNIFICANT changes in the treatment of meningococcal infections have been brought to the attention of most medical officers who have been on duty in station hospitals in the United States during the past year. As the result of a number of epidemics of meningococcal meningitis of sizeable proportions since 1938, several reports¹⁻⁵ on the use of sulfonamides as the sole therapeutic agents have appeared in the literature. Their use was further emphasized by War Department Circular No. 17, dated 23 February 1942 issued by the Surgeon General's Office. Data accumulated from a variety of sources—(1) personal communications from members of the Preventive Medicine Division of the Surgeon General's Office, (2) from the Medical Consultant of the Sixth Service Command, (3) from Chiefs of the Medical Services of other Station Hospitals, and (4) from reports in the literature—

indicate that sulfadiazine and its sodium salt is the drug of choice because of its high degree of therapeutic efficiency, its low toxicity, and the infrequency with which complications appear after its use. Our own experience with 61 cases seen and treated at this Station Hospital bears out these observations and serves as the basis for this report.

Epidemiology. Between December 12, 1942 and July 29, 1943, 61 cases of meningococcal infection were admitted to the Station Hospital, Camp McCoy, Wis.; 58 of these patients were soldiers and 3 were civilians. Epidemiologic factors were in accord with those usually

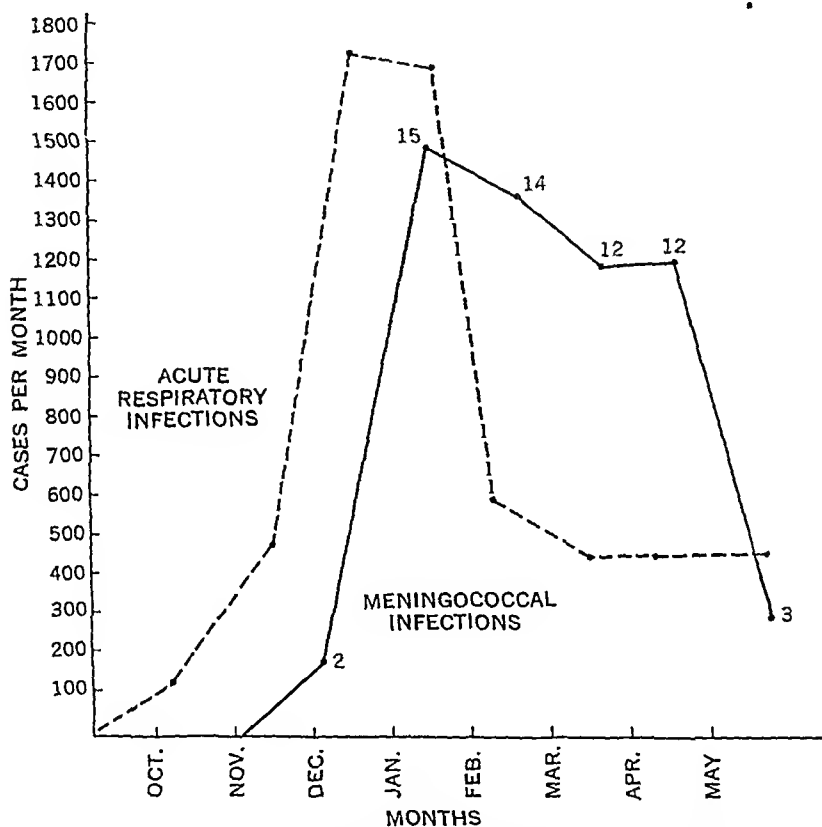


CHART 1.—Cases of acute respiratory infection and meningococcal infection admitted to hospital per month.

recorded: (1) there was no evidence of cross-infection because in no instance did more than one case appear in a single barracks or company; (2) 82% of the soldier-patients were raw recruits; their average age was 23 years and their average time of service was 2.7 months; (3) there had been unusual exposure to severe weather conditions in many instances; (4) there was a degree of overcrowding, impaired ventilation, and increased fatigue. A survey for meningococcus carriers was deemed impractical because of lack of adequate laboratory facilities, nor was it believed that such a survey would serve any useful purpose. Sixty to 70%⁴ of the population has been found to

TABLE 1.—SUMMARY OF 53 CASES OF MENINGOCOCCAL MENINGITIS

Patient	Age	Months of service	Duration (days)	Upper respiratory infection			Head-ache	Myalgia	Arthral-gia	Rest-lessness	Vomit-ing	Nuchal rigidity	Kernig	Apathy	Coma	Respi-ratory rate	Admis-sion temp.	Rash
				Chill†														
1	20	28	1	+	+	+	+	0	+	+	+	+	+	0	0	26	104	0
2	22	2	1*	0	+	+	+	+	+	+	0	+	0	0	0	24	101	0
3	28	2	2	+	+	+	+	+	+	+	+	+	0	0	0	24	98	0
4	21	2	1	+	+	+	+	0	+	+	+	+	+	0	0	32	103	0
5	32	2	1	+	+	+	+	0	+	+	+	+	+	0	0	32	101	0
6	21	4	1	+	+	+	+	0	+	0	+	+	0	0	+	28	99	0
7	21	2	1	+	+	+	+	+	0	0	+	0	0	0	0	24	98	0
8	37	1	1	0	+	+	+	+	+	0	+	0	0	0	0	28	99	0
9	23	7	1	+	+	+	+	+	0	+	+	+	+	0	0	26	98	0
10	33	8	1	+	+	+	+	+	0	+	+	0	0	0	0	32	103	0
11†	25	1	1	+	+	+	+	+	0	+	+	0	0	+	0	24	101	0
12	22	1	1	0	+	+	+	+	+	0	+	+	0	0	0	30	100	0
13	21	1	1	+	+	+	+	+	0	+	+	+	+	0	0	26	102	0
14	24	1	1	+	+	+	+	+	0	+	+	+	+	0	0	28	102	0
15	25	1	1	+	+	+	+	0	+	+	+	+	+	0	0	22	101	0
16	25	25	1	+	+	+	+	+	0	+	+	+	+	0	0	24	101	0
17	25	14	1	+	+	+	+	+	0	+	+	+	+	0	0	30	100	0
18	21	8	1	+	+	+	+	+	0	+	+	+	+	0	0	22	100	0
19	20	1	1	+	+	+	+	0	+	0	+	+	+	0	0	22	100	0
20	21	4	1	+	+	+	+	0	+	0	+	+	+	0	0	28	103	0
21	32	2	2	+	+	+	+	0	+	0	+	+	+	0	0	24	100	0
22	21	4	1	0	+	+	+	0	+	0	+	+	+	0	0	26	104	0
23	19	1	1	+	+	+	+	0	+	0	+	+	+	0	0	24	99	0
24	23	24	1	+	+	+	+	0	+	0	+	+	+	0	0	24	99	0
25	21	1	1	+	+	+	+	0	+	0	+	+	+	0	0	24	101	0
26	40	5	2	+	+	+	+	0	+	0	+	+	+	0	0	26	103	0
27	23	2	2	0	+	+	+	0	+	0	+	+	0	0	0	24	103	0
28	20	2	1	+	+	+	+	0	+	0	+	+	0	0	0	16	97	0
29	26	48	1	0	+	+	+	0	+	0	+	+	0	0	0	16	97	0

[illegible]

* Less than 1 day.

+ Acute fulminating meningococcal septicemia without meningitis.

- Definite rigor or recurrent chilly sensations.

Demerol
Average.

Percentage of cases showing respiratory rate above 20.

carry the meningococcus at the peak of an epidemic and the premise that the elimination of the carrier would terminate an epidemic is entirely theoretical and impractical to effect.

Late in November, 1942 an epidemic of acute respiratory infection had its inception and reached its peak in December, 1942 and the first 3 weeks in January, 1943. The terminal phase of this peak of case incidence coincided with the onset of the meningitis epidemic as indicated in Chart 1. From these observations it seems probable that there was a close association between the epidemic of upper respiratory infection and the epidemic of meningococcal infection. This is contrary to the belief of many epidemiologists.

Clinical Aspects. The clinical picture presented by patients suffering from meningococcal infections is protean and varies from one of an overwhelming generalized sepsis with collapse, associated with the Waterhouse-Friderichsen syndrome, to that of a mild evanescent type of infection associated with generalized aching, slight aching, slight fever, a few skin lesions, and with bacteremia. As a result of the differences in the clinical features, we have elected to divide our cases as follows: (1) the acute meningococcal septicemia with meningitis (51 cases), (2) acute meningococcal septicemia without meningitis (2 cases) and (3) acute evanescent meningococcemia (8 cases). The last group of cases in contrast to the aforementioned fulminating types are exceedingly mild, and are, as will be shown in another paper, self-limited. It is our opinion from a review of the literature on epidemic cerebrospinal meningitis that the features of those cases with evanescent meningococcal bacteremia have not been sufficiently emphasized.

It is not within the scope of this paper to discuss the signs and symptoms of meningococcal meningitis in detail, however, the essential findings at the time of admission in the cases herein reported are tabulated in Table 1. All of the commonly described signs and symptoms were observed; and, in addition, there was encountered with a striking degree of frequency a sign which the authors have not heretofore seen included in textbooks nor in treatises relating to this disease. In almost all cases (53 of the 61) there appeared an unusual increase in the respiratory rate. In fact, tachypnea introduced a confusing situation in a few cases, without evidence of marked meningeal irritation, in that when it was associated with fever, chill, mild headache, and leukocytosis, pneumonia was simulated. There was no relationship between the height of the temperature and the respiratory rate, since of 10 cases admitted with an average temperature of 98.2, the average respiratory rate was 24.6 per minute.

In this series of 61 cases, at the time of admission, signs and symptoms were observed (see p. 483) in the 51 cases of acute meningococcal septicemia with meningitis and 2 cases of acute meningococcal septicemia without meningitis:

The laboratory data are presented in Table 2. Although meningococci may be recovered from the nasopharynx, the blood, or from the spinal fluid at the onset of meningitis, our bacteriologic study did

not include examination of specimens obtained from the nasopharynx. Of the 51 cases of meningitis, the cerebrospinal fluid was cloudy on admission in 47 cases. In patients Nos. 15, 22, 40, and 42 the spinal fluid contained 64, 22, 8, and 10 cells respectively on admission, but became grossly cloudy and contained 11,700, 14,200, 12,400 and 1,750 cells respectively on the 2nd hospital day. Gram-negative intracellular diplococci were demonstrated in stained smears of the cerebrospinal fluid in 36 cases, or 71% of those in which lumbar punctures were made. From the cerebrospinal fluid, positive cultures of *Neisseria intracellularis* were obtained in 33 cases, a percentage rate of 65. The blood culture was positive in 28 cases (53%) of the patients with meningitis. With direct smear of the spinal fluid, culture of the spinal fluid and the blood culture, laboratory confirmation of meningococcal infection was obtained in 47 cases (90%). In 28 instances meningococci were identified as Type 1. In one case Type 2A was present.

SIGNS AND SYMPTOMS OBSERVED

(The respiratory rate was not recorded in 2 cases)

	No. of cases
Tachypnea	47
Headache	45
Chill (or chilly sensation)	31
Generalized aching	40
Vomiting	38
Arthralgia	13
Nuchal rigidity	46
Positive Kernig	36
Restlessness	21
Apathy	14
Coma or semi-coma	14
Delirium	4
Petechiae	32
Purpura	4

In view of the fact that demonstration of the organism has been possible in 90% of our cases, a brief description of the cultural methods utilized seems indicated. Details of the method will be published elsewhere.⁶

Blood Culture. Ten cc. of the patient's blood is added to 150 cc. of sterile tryptose phosphate broth. The inoculated flasks are incubated at 37° C. and are observed at intervals for bacterial growth for at least 2 weeks. On occasion, growth has been noted for the first time after 2 weeks.

Spinal Fluid Culture. (a) Spinal fluid is inoculated on chocolate blood agar plates, placed in an atmosphere of 10% carbon dioxide and incubated at 37° C. for from 1 to 2 days. (b) One cc. of spinal fluid is added to 10 cc. of sterile Bacto-Tryptose-Phosphate broth. (c) One cc. of spinal fluid is added to modified Tryptose-Maltose-Carbonate broth. The inoculated tubes are incubated at 37° C. in an atmosphere of 10% carbon dioxide for 1 to 2 days and are observed for bacterial growth.

It is imperative that both the blood and spinal fluid be immediately inoculated into the culture media at the bedside.

TABLE 2.—SUMMARY OF FINDINGS IN 53 CASES OF MENINGOCOCCAL MENINGITIS*

Patient	Cerebrospinal fluid										Blood		Urine hematuria	Total		1st 5 days		Total days treatment
	Cell count	% polys.	Culture	Sinear	Culture	Initial W.B.C.	% polys.	Total		S.D. and S.S.D.	S.D. blood level							
								S.S.D.†	S.D.									
1	9,220	92	0	+	+	13,000	79	0	12.5	76	64.5	24.1	10					
2	7,450	93	0	+	+	6,800	65	+	15.0	56	41.0	9.2	17					
3	1,880	88	0	+	0	22,700	91	0	15.0	106	75.0	17.4	13					
4	995	92	0	+	0	22,000	86	+	8.5	52	60.5	21.5	5					
5	2,800	94	+	0	+	12,000	79	0	13.5	43	56.5	17.5	5					
6	2,300	98	+	+	0	7,600	57	+	15.0	40	43.0	9.3	8					
7	30,000	95	+	0	+	10,900	70	0	5.0	48	39.0	11.8	7					
8	44,000	91	0	+	0	14,600	79	0	10.0	106	68.0	13.9	16					
9	7,350	98	+	+	+	24,100	77	+	10.0	68	44.0	16.6	13					
10	15,400	0	0	+	0	35,000	91	+	13.5	120	75.5	19.5	13					
11	13,900	96	+	0	0	11,700	85	+	20.0	93	62.0	16.8	15					
12	3,100	94	+	+	+	13,600	86	+	15.0	66	45.0	17.3	12					
13	5,600	94	0	+	+	44,700	83	+	13.5	82	59.5	17.5	11					
14	64†	90	+	0	0	15,200	79	+	23.5	85	66.5	10.5	13					
15	6,700	89	+	+	0	24,100	77	0	15.0	60	39.0	13.9	11					
16	17,800	88	+	0	0	18,700	81	+	8.5	81.5	58.0	15.8	12					
17	5,000	95	0	0	0	10,800	52	+	15.0	76	51.0	16.5	9					
18	2,850	89	+	0	0	30,090	87	+	5.0	83	53.0	16.2	10					
19	3,050	96	+	+	+	32,700	90	+	13.5	73	69.5	15.3	10					
20	6,600	87	+	+	+	31,430	84	+	15.0	65	64.0	21.7	9					
21	22†	9	+	0	+	10,150	61	+	10.0	70	58.0	13.8	10					
22	1,500	94	+	+	+	34,500	81	+	10.0	69	55.0	11.9	11					
23	2,400	95	+	+	+	15,450	80	+	5.0	68	49.0	12.0	11					
24	6,850	79	+	+	+	19,700	83	0	5.0	74	53.0	12.5	11					
25	12,350	95	+	0	0	27,100	93	0	5.0	76	58.0	12.0	10					
26	5,500	88	+	+	0	14,300	88	0	5.0	68	57.0	15.4	9					
27	5,500	88	+	+	0	28,550	95	+	42.5	52	57.0	15.4	9					
28	5,500	88	+	+	0	17,400	95	+	42.5	52	57.0	15.4	9					

29	1,250	97	+	+	+	+	16,450	84	0	53.0	11.8	8
30	292	90	+	+	+	+	25,200	84	+	60.0	12.4	13
31	750	96	+	+	+	+	23,650	86	+	58.0	13.1	11
32	7,750	97	0	0	0	0	17,500	93	0	51.0	15.9	8
33	7,750	97	0	0	0	0	13,400	87	0	61.0	13.4	6
34	22	0	0	0	0	0	17,200	84	0	64.0	12.3	10
35	14,200	97	+	+	+	+	33,600	85	0	50.0	10.5	11
36	5,800	95	+	+	+	+	17,050	81	0	68.0	13.8	9
37	3,500	96	0	0	0	0	19,850	68	+	51.0	13.5	10
38	10,000	38	+	+	+	+	11,650	86	+	55.0	13.8	9
39	11,600	96	0	0	0	0	19,700	88	+	45.0	17.4	10
40	8†	0	0	0	0	0	24,750	91	+	58.0	14.3	6
41	12,000	95	+	+	0	+	9,650	69	+	38.0	15.6	10
42	10‡	0	0	0	0	0	16,750	89	+	55.0	14.4	7
43	850	98	+	+	+	+	36,000	93	+	53.0	17.9	8
44	1,300	95	0	0	0	0	17,350	84	0	62.0	18.9	6
45	12,950	97	0	0	0	0	28,550	54	0	11
46	4,750	98	+	+	+	0	26,600	88	0	52.0	21.3	9
47	10,300	93	+	+	0	0	10,300	93	0	52.0	21.2	8
48	570	50	+	+	+	0	11,000	78	0	39.0	22.0	9
49	35,700	98	+	+	+	-	6,500	26	0	8
50	8,750	96	0	0	0	0	18,150	30	0	13
51	6,600	97	0	0	+	0	29,050	89	0	70.0	13.4	9
52	17,550	89	+	+	0	0	17,850	77	0	111	19.6	15
53	1,000	54	+	+	0	0	17,200	82	0	55.0	14.4	7
Av. or %	9,440	92%	65%	71%	53%	53%	19,768	80	53%	55.7	15.2	10

* Cases No. 11 and No. 34 were acute fulminating meningococcal septicemia without meningitis.

† Sodium sulfadiazine; S.D. = sulfadiazine.

‡ Case Nos. 15, 22, 40 and 42 showed 11,700 cells with 91% polys; 14,200 cells with 94% polys; 12,400 cells with 98% polys and 1750 cells with 84% polys on lumbar puncture on second hospital day respectively.

§ 3 infants on whom sulfadiazine levels were not done.

Para-amino-benzoic acid was used for the purpose of inhibiting the action of the sulfadiazine when it had been used in 2 cases prior to obtaining blood and spinal fluid for culture. However, no growth resulted.

Diagnostic Procedure and Treatment. All patients suffering from meningococcal infections should be considered as potentially seriously ill. In order to obviate confusion resulting from a swiftly changing personnel and assist ward officers newly arrived and, therefore, unfamiliar with the hospital routine in dealing with patients suspected of suffering from meningococcal infection, the following outline was prepared:

1. Notify the laboratory that a specimen of cerebrospinal fluid is to be withdrawn by lumbar puncture. The laboratory furnishes:

- (a) 1 sterile glass tube with cotton stopper
- (b) 1 tube of sterile Bacto-Tryptose-Phosphate broth
- (c) 1 tube of modified Tryptose-Maltose-Carbonate broth
- (d) 1 chocolate blood agar plate
- (e) 1 flask of Bacto-Tryptose-Phosphate broth for blood culture

If the patient has received any sulfonamide the laboratory is notified in order that it should furnish media to which has been added para-amino-benzoic acid.

2. Complete blood count is requested.

3. Urine specimen to be obtained if patient can void.

4. Directions for lumbar puncture. This procedure will not be initiated until the specimen tubes and media arrive from the laboratory. Strict surgical asepsis will be carried out. The fluid will be permitted to escape slowly. Allow 10 to 15 drops to fall directly into each of the 2 test tubes containing the broth media, 5 drops on the blood agar plate and about 5 cc. into the empty sterile test tube.

If the spinal fluid is cloudy, or if in the opinion of the medical officer the patient is suffering from a meningococcal septicemia, the following therapeutic procedure will be immediately instituted:

5. Five gm. of sodium sulfadiazine are dissolved in 100 cc. of sterile distilled water and injected slowly intravenously, using a salvasan set. If the patient is unconscious a second 5 gm. of sodium sulfadiazine will be given 8 hours later.

6. Sulfadiazine, 2 gm. every 4 hours. Start the oral medication upon completion of the injection of sodium sulfadiazine.

7. One hour after the administration of sodium sulfadiazine 1000 cc. of 5% glucose in physiologic salt solution will be given intravenously.

8. Sufficient fluid intake by mouth or/and intravenously will be administered to secure a minimum daily output of urine of 1500 cc.

9. For 5 days daily determinations of the blood concentration of sulfadiazine will be made and every 48 hours thereafter as long as the patient is receiving the drug.

10. White blood counts and differential counts will be made every other day as long as the patient is receiving the drug and twice weekly throughout the period of hospitalization.

11. The blood concentration of sulfadiazine will be maintained at a level of 12 mg. per 100 cc. for 5 days.

12. Urinalysis will be made every 2nd day.

13. A culture of the nasopharynx for meningococci will be made 3 days prior to the expected date of discharge.

Sulfadiazine and sodium sulfadiazine were the sole chemotherapeutic agents used in all cases with the exception of Cases 12, 14, and 15, which were given in addition to chemotherapy, 30 cc., 30 cc., and 90 cc. of polyvalent meningococcus antiserum, respectively. It was believed that no favorable response resulted from the use of antiserum in Cases 12 and 14 and in Case 15 the response was equivocal.

Sulfadiazine and its sodium salt appeared to effect a cure in all cases. Both drugs were used in all cases with the exception of the 3 infants. The initial intravenous dose of sodium sulfadiazine was 5 gm. and the average total dose of this drug was 10.01 gm. Fourteen of the cases received only 5 gm. but 11 required 15 gm. or more because of persistent vomiting or the failure of the sulfadiazine blood level to rise adequately early in the course of the disease. The total amount of sulfadiazine administered orally varied considerably. The average total dose was 62.5 gm.; the minimal amount was 40 gm. and the maximal amount was 120 gm. Our observations lead us to believe that most of the cases had practically recovered by the 6th hospital day. The study by Banks² of spinal fluid taken 12, 24, and 48 hours after the diagnostic puncture, demonstrated that bacteriostasis was effected in 24 hours, that phagocytosis of free organisms had taken place and that within 48 hours the process of absorption of the exudate was well advanced when sulfathiazole was used. In view of these observations and in the light of our own clinical observations, an analysis of the amount of sulfadiazine and its sodium salt given and the sulfadiazine blood level determinations during the first 5 hospital days seems warranted. The amount of *sodium* sulfadiazine has already been noted and these figures will not be repeated since all of this drug was administered during the first 5 days of hospitalization. The amount of sulfadiazine given orally varied from 24 gm. to 66 gm., with an average amount of 44.6 gm. However, the minimum total amount of sulfadiazine and its sodium salt was 38 gm., the maximum was 75.5 gm. and the average was 55.7 gm. during the first 5 days of treatment. The blood sulfadiazine level was obtained almost daily for 5 days on all cases. In some instances when the blood level was unusually high or low, a second determination was made the same day. The lowest average blood level was in Case 2, 9.2 mg. per 100 cc.; the maximum was in Case 1, 24.1 mg.; and the average for the first 5 day period for all cases was 15.2 mg. The total number of days of treatment varied from 5 to 17; in 62% of the cases the therapy was given for a period of 10 days or less. The average for all cases was 10 days.

Only 1 serious complication, namely agranulocytosis, was encountered as a result of sulfadiazine therapy. This occurred, perhaps by coincidence, in Case 10, who had received the largest dose of sulfadia-

zine of any patient in this series. The white blood count fell from 4600 on the 15th hospital day to 1950 with only 8 neutrophils on the 19th hospital day. However, improvement began 5 days later and he made a slow recovery following the use of blood transfusions, pentnucleotide and adenine sulfate.

Hematuria was noted in 53% of the cases, the cause of which was attributed to the large doses of sulfadiazine. However, gross hematuria was noted in only 3 cases and in no instance did anuria or other serious renal complications occur. Sulfacrystalluria was observed in 9 cases.

The symptomatic treatment did not vary from that which has been recommended by others with the exception that we have used morphine rather freely for the control of severe headache and extreme restlessness when bromide and chloral or barbiturates did not succeed in controlling these symptoms.

We encountered 2 patients in whom acute meningococcal purulent arthritis was a complication. This complication will be dealt with in another communication.

Discussion. Factors that are responsible for converting the carrier into the disease state are still unknown. However, it is interesting to note that in 68% of our cases, a history of an antecedent upper respiratory infection was present and that the onset of the meningitis epidemic followed the peak of a severe epidemic of upper respiratory infection. It is obvious that the disease is not highly contagious, since in no instance was there evidence of cross-infection.

Although it is customary and required to assess the severity of the disease at the time of admission, we feel strongly that every case should be regarded as potentially seriously ill. The picture of a "mild" case of meningococcal meningitis characterized by headache, slight fever, generalized aching, and nuchal rigidity in an individual who does not appear severely ill can change so rapidly into a comatose or semi-comatose patient with generalized purpura, convulsions, and extreme collapse that an evaluation of their status at the time of admission is of no consequence.

On admission the clinical features of meningitis were similar in most cases and occurred in the course of, or following, an acute respiratory infection. Notable exceptions were in the following: Patient 52 complained of left lumbar pain of such severity that he was surveyed temporarily, but briefly, on the urologic service for a suspected urinary calculus. The chief complaint of Patient 8 was severe epistaxis, and in Patient 34 the swollen, painful joints were conspicuous features. The coexistence of contagious diseases is rare, but in Patient 48 meningitis and mumps with probably mumps encephalitis occurred. On admission he had severe bitemporal headache and nausea for 36 hours; except for pharyngeal mucosal injection and suggestive nuchal rigidity, the physical examination was negative. The white blood cells numbered 11,000 with 78% neutrophils. On lumbar puncture the cerebrospinal fluid was grossly clear but contained 570 white blood cells with 50% neutrophils and 50% lymphocytes. The following

morning bilateral parotitis developed. At this time a second lumbar puncture was done. The spinal fluid contained 232 white blood cells, 77% of which were neutrophils. This case occurred during a period when mumps was prevalent. That mumps encephalitis coexisted in this patient seems highly probable in view of the fact that the differential spinal fluid count showed 50% lymphocytes, an observation noted in only 1 other apparently uncomplicated case. Fortunately, a stained smear of the spinal fluid on admission was positive for gram-negative intracellular diplococci.

A study of these 53 cases, together with the 8 cases of evanescent meningococcal bacteremia to be reported elsewhere, makes it evident that the pathologic evolution of the disease is characterized by an initial infection in the nasopharynx following which the organisms migrate to the blood stream. From the blood, invasion of the tissues results. That meningitis is not an invariable occurrence as a sequel to meningococcal bacteremia is evident, since in 4 of the aforementioned 8 cases the etiologic agent was not discovered for from 3 to 6 days following the time of admission and at the time the patients were recovering from their untreated bacteremic disease. Although the symptoms and findings in the nervous system tend to obscure other focal manifestations of septicemia, more emphasis should be placed on the latter to facilitate earlier recognition and the institution of treatment before meningitis ensues.

No time should be lost in instituting immediate chemotherapy in large doses. From the reports in the literature, we have the impression that many of our cases could have been successfully treated by giving the drug by the oral method without resorting to the intravenous method. Nevertheless, there are many advantages in initiating the therapy by the intravenous method. A few hours of valuable time is gained since it is now generally accepted that the drug given by mouth is absorbed rather slowly and is not followed by a rapid rise of the drug content in the blood. The importance of obtaining a high blood level of sulfadiazine early in the course of treatment of pneumonia has been clearly shown.⁶ To obtain a high blood level quickly, requires the use of sodium sulfadiazine administered intravenously. The average sulfadiazine blood level taken within 8 to 12 hours following the intravenous injection of 5 gm. of sodium sulfadiazine and a variable amount of peroral sulfadiazine (from 2 to 6 gm.) was 13.3 mg. per 100 cc. The results obtained with the combined intravenous use of sodium sulfadiazine and the peroral use of sulfadiazine have led us to conclude that this method is therapeutically effective and is the treatment of choice in meningococcal infections.

Summary and Conclusions. An epidemic of 61 meningococcal infections occurred following a wave of acute respiratory infections. The latter seemingly bore a direct relation to the onset and progress of the epidemic of meningococcal infections. Eighty-six per cent of the cases developed among raw recruits.

In 51 cases of acute meningococcal septicemia with meningitis and 2 cases of acute fulminating meningococcal septicemia without men-

ingitis, all of the commonly described signs and symptoms were encountered, but in addition to these findings, tachypnea was noted in 88% of the cases.

The initial treatment should routinely consist of sodium sulfadiazine intravenously and repeated in those cases where the oral administration of sulfadiazine is not feasible. There were no fatalities among the 53 cases reported in this series and the additional 8 cases of acute evanescent meningococcal bacteremia to be reported also survived.

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BURN TRAUMA PRECIPITATING ACUTE LEUKEMIA OR A LEUKEMOID CONDITION

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AND

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THE subject of the interrelationship of trauma to acute myelogenous leukemia poses an interesting problem. Recently, a patient under treatment on our surgical service for extensive burns suddenly presented the picture of a blood dyscrasia, which terminated fatally.

It is difficult to evaluate the wide variety of opinions of the factors involved in the possible etiology of acute leukemia. Before attempting to do so, it is important to consider whether the disease is of infectious or neoplastic origin. MacCallum¹¹ presented the view that acute leukemia has the appearance of an acute infectious process, wherein one finds hemorrhages, and necrotic and ulcerative stomatitis as a common occurrence. Sternberg¹⁶ suggested that myeloblastic leukemia be separated from the other leukemias, and be regarded as purely infectious in nature; since the pathologic picture is so striking in similarity to infection, moreover some severe infections cause the appearance of numbers of myeloblasts and myelocytes. Hirsch⁸ concluded that infection plays a major rôle in the etiology of all cases of acute leukemia. The basis for this belief is that acute myelogenous leukemia is associated with fever, toxemia, chills and other manifestations of an infection. In addition, infections are often associated with this blood dyscrasia.

Many maintain the opposite view. Piney¹⁴ concluded that leukemia is a neoplasm. Dimmel,⁵ and likewise DeCastello,⁴ stated that the

leukemic process was not an infection and could not be identified with sepsis. The feeling was that a process that spreads and involves other organs forming hematogenous metastases cannot be regarded as hyperplastic but rather as neoplastic. Likewise, Cecil³ preferred that leukemia be catalogued in the category of neoplasias rather than that of infections, maintaining that it is a fatal invasive pathologic process. True, up to the present time, against the infectious theory for acute leukemia are the facts that no organism has been recovered, the disease has not been reproduced experimentally, and the disease has not been transmitted from one animal to another.

It is evident from the foregoing that no conclusion as to the validity of either theory can be made. However, a number of authors have reported cases wherein the occurrence of trauma preceding the onset of leukemia has possibly been more than a coincidence. Rubnitz¹⁵ offered the possibility that splenic trauma may cause acute myelogenous leukemia. Olovson¹³ collected 67 cases wherein leukemia occurred in association with trauma to the spleen and long bones. His discussion did not include cases of rupture of the spleen which were pathologic complications of leukemia. Lewson¹⁰ conceded that trauma to the hemolytopoietic organs does not always cause leukemia; but believed that in individuals with an inherent predisposition, leukemia may first appear following such trauma. The relationship seems analogous to that of special kinds of trauma in the production or stimulation of sarcomas and carcinomas. On the other hand, Ewing tended to exclude trauma as a possible causative factor in leukemia.

Yaguda and Rosenthal¹⁸ have cited the criteria as set down by Liniger which would establish the corelationship between trauma and leukemia. In essence they do not differ from those proffered by Olovson; namely, that the individual must have been free of disease symptoms prior to the trauma, a suitable severe injury must have occurred, and a lag period must elapse between the injury and the disease.

In the literature, apparently, trauma to the long bones with or without fracture, trauma to the spleen or splenic areas with or without rupture, or trauma which causes severe generalized body concussion, have been the only types of trauma suggested as possible etiologic factors in leukemia. The case we are reporting is one in which a picture quite similar to that of myelogenous leukemia appeared shortly after a severe cutaneous burn.

Case Report. *History of Present Illness.* A soldier, age 28, black, was admitted to the hospital on August 21, 1943. On the morning of admission, the soldier had lit a gasoline field stove preparatory to cooking breakfast. The flame was so excessive that he was unable to reach the valve to diminish it. When attempting to sprinkle sand on the burner, the gasoline tank of the stove exploded showering the soldier with burning gasoline. The blaze was smothered by wrapping him in blankets.

Past and Family History. Past history gave no indication of any previous physical abnormalities or hint of any disease process either acute or chronic. There was no contributory family history.

Physical Examination. The soldier appeared his given age and was well developed and well nourished. He was in apparent shock on admission, which

was 1 hour after the accident. There was wide distribution of burned areas—second, third and fourth degree—of the forehead, face, both ears, both shoulders both forearms and hands, both lower extremities from ankles to groins. The estimated surface area of burn was calculated according to Berkow's method¹, to be approximately between 55 and 60%. Pulse on admission was 120, and blood pressure 122 systolic and 72 diastolic. Other physical findings were essentially negative.

Laboratory Data. On admission, the blood count was normal, 4,800,000 R.B.C., 85% hemoglobin, 12,000 W.B.C. (69% neutrophils, 25% lymphocytes and 6% monocytes). The hematocrit was 59% (Hayden's method). Urinalysis: specific gravity of 1.028, amber color, acid reaction, an occasional R.B.C. Sedimentation rate was 1 mm. (Cutler).

Treatment and Progress. Shock therapy was instituted in accordance with accepted authorities. One-half grain of morphine sulfate was administered hypodermically. During the first 24 hours 3000 cc. of plasma was infused. The burned areas were quickly and carefully débrided under aseptic precautions. Within the second 24 hours, 1350 cc. of plasma and 3 cc. of adrenal cortex in divided doses was given, followed on the 3d day by 650 cc. plasma and 2 cc. adrenal cortex. The fluid intake *per os* was augmented by infusions of either glucose-saline or glucose-water combinations.

The condition of patient was progressing satisfactorily. Sulfadiazine in small doses was administered as a precautionary measure against infection. The burned areas epithelized rapidly. The soldier was taking nourishment well and was mentally alert.

CHART I.—ILLUSTRATING PERIPHERAL BLOOD PICTURE ON VARIOUS DAYS OF ILLNESS

Date	R.B.C.	Hgb.	W.B.C.	Seg.	Juvenile stabs	Metamyelocyte	Premyelocyte	Myeloblast	Myelocyte	Eosinophil	Basophil	Lymphocyte	Monocyte	Normoblast	Hematocrit	Remarks
8/21/43	4.78	85	12,150	03	6							25	6		59	
8/22/43	4.24	85	16,650	62	8					1		20	9		55	
8/25/43	3.82	70	14,500	66	5					1	1	21	6		39	
8/28/43	2.68	65	50,200	50	35		1	4				8	2		30	Toxic granules in neutrophils
8/29/43	2.42	60	65,300	37	41		5	3	1	1		9	3	6	30	Macrocytosis, polychromatosis
8/30/43	2.21	55	88,500	50	20	7	4	3	2			10	4	10	28	"
8/31/43	2.68	55	83,200	42	28	5	1	4	7			9	4	5	30	"
9/1/43	2.51	60	81,000	23	38	2	9	6	6	1	1	11	3	9	28	"
9/2/43	2.46	55	137,000	34	32		4	9	4		1	13	3	5	28	"

BONE MARROW STUDY

Date	Myelo-blasts	Pre-myelocyte	Myelo-cytes	Juvenile Stabs	Polys.	Monos.	Eos.	Macro-blasts	Normo-blasts
9/2/43	76	3	11	6	2	1	1	15	21

On the 8th day of his illness, there was a decided alteration in his blood picture (Chart I), though clinically his general condition seemed to be progressing favorably. This was the initial indication that, regardless of his apparent improvement, something radical was occurring in his hemolytopoietic system. From the 9th day to his death on the 13th day, his condition rapidly deteriorated despite treatment. On the 11th day after admission the soldier was restless and desired to get out of bed. The following day he appeared brighter and more coöperative. During the morning of the day of his death, he became noisy and unmanageable, finally going into a coma 2 hours before termination. Several blood transfusions were given, but the reaction of the hemolytopoietic system was irreversible. The white cell count of the peripheral circulation, prior to death, had reached a level of 137,800 (including 4 myelocytes, 4 premyelocytes and 9 myeloblasts). Towards the end of the case, a bone-marrow study revealed 76% myeloblasts, 3% premyelocytes, 11% myelocytes, 2% segmented neutrophils, 6% juvenile and stab forms, 1% monocytes and 1% eosinophils.

Necropsy. The findings were very meagre. The lungs were not involved in any pneumonic process, the arteries and veins contained blood in which the erythrocytes were reduced in number. However, the white blood cells were numerous and displayed a mark shift to the left. There was nothing noteworthy in the heart, aorta, gall bladder, brain and adrenals. Cloudy swelling (albuminous degeneration) was noted in the liver, spleen, kidneys, lungs and pancreas. The spleen was only slightly enlarged. Damage to the hemolytotoxic system was evidenced throughout with a decided shift of the granulocytes to the left.

Discussion. The case presented is that of a young man, who up to this accident was apparently healthy, carrying on the normal arduous duties of a soldier with complete satisfaction to his superiors. In the $1\frac{1}{2}$ years of his army career, this was his only hospitalization. On his admission to this institution, his blood picture was normal; as time progressed his burned areas were healing satisfactorily, and then when recovery was in the offing, his blood picture became chaotic. One may or may not be inclined to ascribe this solely to a leukemoid reaction, which Krumbhaar⁹ first described some years ago; wherein, in some extreme infections and a few other conditions, one may find huge numbers of myeloblasts, myelocytes and neutrophils circulating in the blood, only to disappear as the infection clears. Again, Goldbloom *et al.*⁷ reported cases of leukemoid reactions caused by sulfapyridine, but here one must keep in mind the possible effects of the benzene ring drugs. Likewise, Moody and Knouf¹² cite similar occurrences which were alleviated by blood transfusions. However, in our case there was no appreciable infection, and furthermore, the injury to the hematopoietic system was so great that the reaction was irreversible.

Stitt *et al.*¹⁷ asserted that leukemia is often a perverted response to the stimulus of infection and often cannot be differentiated sharply from cases with leukemoid reaction. Consequently, the question arises—where do leukemoid reactions end and leukemia begin? Of course if one accepts leukemia as neoplastic, then, as there is a great variety of carcinogenic stimuli, the differentiation is difficult and must depend on the course of the case. If the patient recovers, and the blood picture reverts to normal, then one may justifiably assume that the condition was that of a leukemoid reaction. However, if the patient presenting no manifestations of other disease processes fails to recuperate, and the blood maintains its perversion as the only major pathologic finding, then it is difficult to accept this irreversible reaction as one of the leukemoid type.

True, as mentioned, the spleen in our case was only slightly, if at all, enlarged. However, in acute leukemia, as Boyd² stated, the spleen may be of almost normal size.

The pertinent contribution of this case is the possible etiology in relation to the burns. According to the criteria as set down by Liniger and also by Olovson, the necessary criteria were present for citing this case as one of traumatic leukemia. All cases previously reported have had an interrelationship of injury either to the spleen or long bones and leukemia. As far as we know, this is the first time where an extensive burn is offered as the possible cause of leukemia. However, this is not wholly the contention of the authors. Of course, one may contend

that this patient, if he had lived long enough, without trauma, might have developed leukemia in any event. We feel that if this patient had so-called latent leukemia, the burn might have served as a "catalyst" in hastening the manifestation of the leukemic process.

Summary. 1. The evidence as to the infectious or neoplastic nature of acute myelogenous leukemia is discussed.

2. Evidence and opinions are cited holding trauma to be a possible etiologic factor in acute leukemia.

3. A case of an extensive burn which terminated with a picture stimulating acute leukemia is presented.

4. The opinion is offered by the authors that trauma, in our case specifically a burn, may be a precipitating agent in the production of leukemia.

We hope that this paper will stimulate further investigation. The relationship of burn trauma to leukemia requires considerable clarification. Also, the question arises whether those patients who have recovered from so-called leukemoid reactions will, if experiencing again with some severe infection or trauma, exhibit once more a tendency toward a perverted blood response.

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USE OF AN AGGLUTINATION-INHIBITION TEST IN STUDYING AN EPIDEMIC OF INFLUENZA

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THE first well-described European influenza epidemic occurred in 1510;⁹ however, it was not until 1933 that the virus etiology of this disease was firmly established by Smith, Andrewes and Laidlaw.¹⁰

Until very recently, the laboratory confirmation of a clinical diagnosis of influenza could be undertaken only at highly specialized centers. In 1941, a simple test for detecting influenzal antibodies was introduced by Hirst.⁵ Now this confirmation can be attempted by clinical laboratories.

During December, 1943, and January, 1944, there was a marked increase in the incidence of respiratory diseases among the military and civilian population of the West Coast of the United States. Clinically most of these were diagnosed as influenza. To aid in its investigation of this epidemic, the Virus Section of the Ninth Service Command laboratory employed a modification of the Hirst test.

The test depends upon the fact that red cells of certain fowls and mammals are agglutinated by both influenza Type A and Type B viruses, and that convalescent human sera specifically inhibit this agglutination. It is therefore referred to as an Agglutination-Inhibition (A-I) test. The technique found to be most satisfactory in this laboratory was based on one described by Burnet.³

Material and Methods. *Collection of Specimens.* Samples of blood were drawn from patients in the "acute" and "convalescent" phases of influenza by the medical and laboratory staffs of the several stations studied. The serum was separated from the clotted blood, and submitted to this laboratory in vials containing small amounts of sulfanilamide as a preservative.⁴ Prior to testing, the sera were kept at ice-box temperature.

Equipment. Flat-bottomed Kolmer racks, Kahn test tubes, 1 ml. serologic pipettes and a water-bath regulated to maintain a temperature of 56° C. were used.

Chicken cells. These were obtained every other day from a local poultry market at the time of slaughter. Blood from the neck veins of single birds was collected in approximately 3 times the volume of 2% sodium citrate. It was immediately filtered through several thicknesses of gauze. The cells were washed twice in 0.9% saline and finally centrifuged at 1500 r.p.m. for 10 minutes. From these packed cells a sufficient amount of a 1.5% suspension was made in 0.9% saline for each day's run. The remaining cells were stored in the ice-box and rewashed before using. They could be kept for several days without seriously interfering with the test.

Virus Suspension. Allantoic fluids containing Type A (PR-8) and Type B (Lee) strains of influenza virus were used. They were prepared by inoculating 10 to 12 day embryonated chicken eggs by the allantoic route with 0.1 ml. of a 10⁻² or 10⁻³ dilution of virus. After 40 to 48 hours of incubation at 36° C., the eggs were placed in the ice-box and the following morning the allantoic fluid was harvested. An average of 7 ml. were obtained from each egg. Agglutination titers of 1 to 320 or above were considered satisfactory. The fluid was frozen in CO₂ awaiting use, however, even at ice-box temperature a workable titer of the virus could be maintained for several weeks. A titration of each virus and a check on the unitage of the prepared suspensions were done each day before starting the tests. To 0.1 ml. of allantoic fluid, 0.9 ml. of saline was added to make a 1 to 10 dilution. Thereafter twofold serial dilutions were made with 0.5 ml. of saline going out to 1 to 2560 (9 tubes). To each tube, containing 0.5 ml. of diluted allantoic fluid, 0.25 ml. of the chicken cell suspension was added. The tubes were shaken a few times by hand and allowed to stand for 1 hour at room temperature. The last tube in which the sedimented red cells did not run on tilting was considered the agglutination end-point. Since in the actual Agglutination-Inhibition test, 8 "agglutinating units" of virus were used, this titer (original dilution) was divided by 8 and a suspension of that strength prepared. After 20 minutes at room temperature the strength of this suspension was checked. To 0.5 ml. of the diluted sus-

pension, 0.5 ml. of saline was added, and twofold dilutions using 0.5 ml. of saline were made. Only 4 dilutions were necessary. To each tube, 0.25 ml. of the chicken cell suspension was added. The tubes were then shaken a few times by hand and read after 1 hour. If exactly 8 "agglutinating units" were not present in the prepared suspension, appropriate adjustments were made by adding more of the allantoic fluid containing concentrated virus or of saline.

Serum. Each specimen of serum was inactivated and serially diluted before testing. To do this 0.125 ml. of serum was delivered into a Kahn tube which was then corked and placed in the 56° C. water-bath for $\frac{1}{2}$ hour. Next, 0.875 ml. of saline was added and twofold dilutions made with saline ($\frac{1}{8}$ to $1:128$). This dilution was made in the first of 2 parallel rows of Kahn tubes, and as it progressed 0.25 ml. of each dilution was delivered to the appropriate tube in the second row. When completed there were 2 rows of test tubes each containing 0.25 ml. of serially diluted serum.

The Agglutination-Inhibition (A-I) Test. Acute and convalescent phase sera from a patient were always tested at the same time in order to avoid variation in behavior of the reagents.⁶ To each tube, containing 0.25 ml. of a serum dilution prepared as in the preceding paragraph, there were added 0.25 ml. of a virus suspension of 8 "agglutinating units" (Type A in the front and B in the rear row) and 0.25 ml. of the 1.5% suspension of chicken cells. The tubes were shaken by hand a few times and then allowed to stand at room temperature for 1 hour. The end-points were read as the original dilution of the serum in which agglutination of the chicken cells by the respective viruses was completely inhibited. Included in each series of tests were Type A and B virus controls in which saline was substituted for the 0.25 ml. of serum, a cell control in which 0.25 ml. of the cell suspension was added to 0.5 ml. of saline, and a serum with a known high agglutination-inhibition (A-I) titer for each of the influenza types. No increase or a single tube increase in the agglutination-inhibition (A-I) titer of a convalescent over an acute phase serum was reported as "negative." An increase of 2 or more tubes (fourfold) was reported as "positive."

Problems Studied and Results. An attempt was made to type all the sera submitted with this Agglutination-Inhibition (A-I) test. The results were then analyzed. The A-I antibody response of individuals to influenzal infection, as well as the overall statistical picture and the epidemiologic tendencies were studied.

During the epidemic, sera from 119 patients clinically diagnosed as suffering from influenza were examined. They came mostly from two stations in central coastal California (Table 1).

Forty-nine of these patients showed a fourfold or greater rise in A-I antibody for influenza Type A. One had such a rise for Type B as well. Because of the unusual nature of this response, sera from this individual were sent to Dr. M. D. Eaton of the United States Army Board for the Investigation of Epidemic Diseases for retesting. He confirmed the rise in antibodies for both Type A and Type B influenza. Similar observations were made by Lennette *et al.*⁸ in the 1941 epidemic, using a complement-fixation technique.

Even though it was soon apparent that the epidemic was due to a Type A virus, all specimens submitted on patients diagnosed as having influenza were tested against both types of virus. This was done in order that any changes in the influenzal pattern might be detected. A few sera from individuals with atypical pneumonia were also tested without revealing evidence of recent influenzal infection.

TABLE 1.—DISTRIBUTION OF CASES OF "INFLUENZA" TYPED BY AGGLUTINATION-INHIBITION TEST

Period	Station 1		Station 2		Station 3		Station 4		Total cases studied	Positive (%)
	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.		
Before Dec. 5	0	1	1	0
Week of Dec. 6	0	1	0	5	6	0
Week of Dec. 13	10	17	5	4	36	42
Week of Dec. 20	14	10	2	3	29	55
Week of Dec. 27	6	4	3	2	15	60
Week of Jan. 3	5	7	1	0	13	46
Week of Jan. 10	0	5	1	3	1	1	11	18
Week of Jan. 17	0	5	1	1	7	14
Week of Jan. 24	0	1	1	0
	35	50	11	15	1	3	2	2	119	41

Not infrequently, the interval between the 2 specimens submitted on each patient was only 2 to 3 days. It was therefore apparent that the earliest and shortest interval in which a rise in antibody could be expected would have to be determined. To obtain this information the results of testing 108 patients were examined on the basis of the

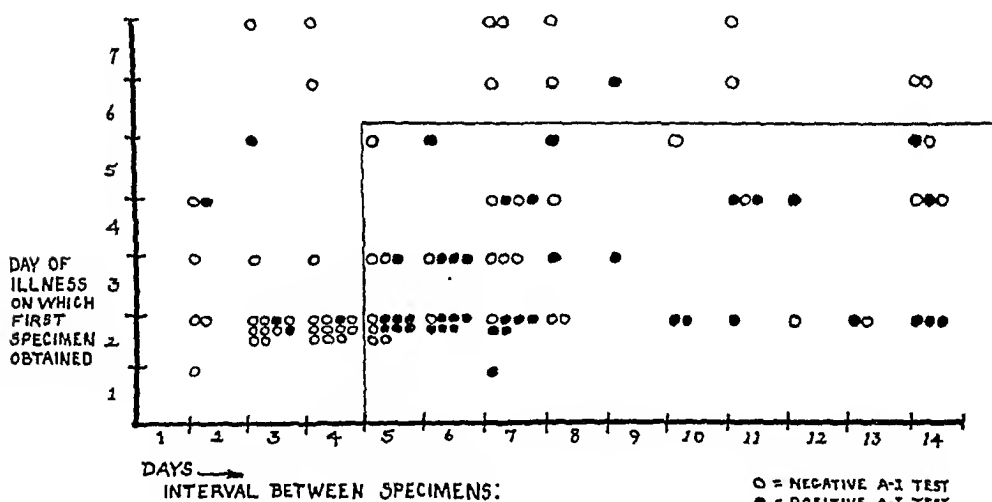


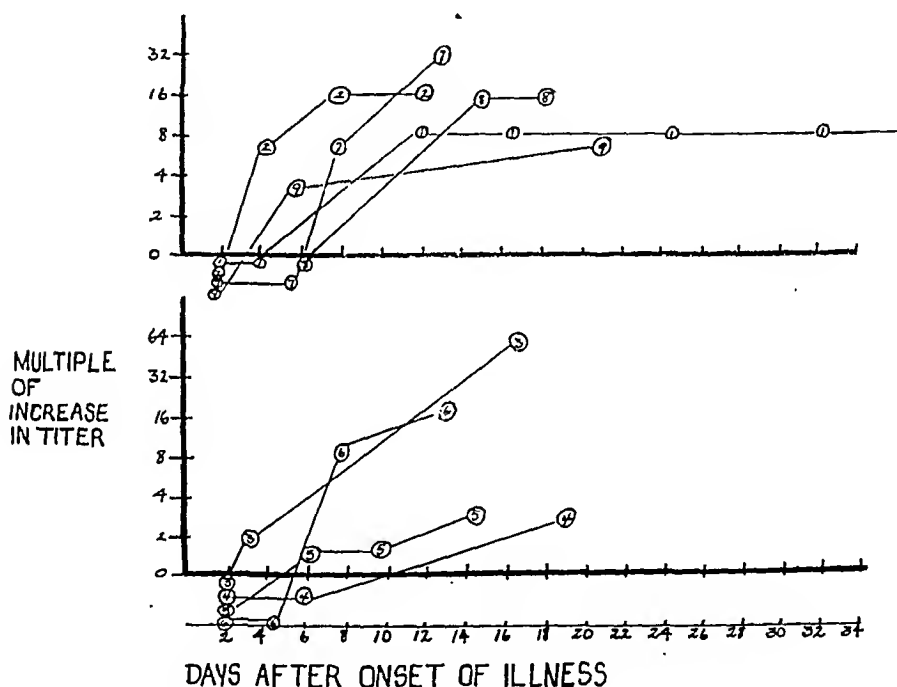
CHART 1.—Relation of day on which specimens collected to type of reaction.

day after onset on which the first specimen was collected and the interval between specimens (Chart 1). A large number of these individuals showed a definite rise in antibody by the end of the first week. There were 65 patients from whom the first specimen of serum was obtained within the first 5 days after onset of the illness, and a convalescent one after an interval of at least 5 days. Among this group, 62% had an influenzal disease which could be typed, in contrast to the 41% among the entire group of patients.

In Graph 1 curves are drawn for 9 patients from whom it was possible to obtain 3 or more specimens. It is apparent that the A-I antibody curve continues to rise after the 1st week. In 2 individuals (4 and 1) who were available for "check-up," antibody levels were

maintained after 6 and 9 weeks, respectively. The different manner in which individuals react to a clinically similar illness is also demonstrated by this graph.

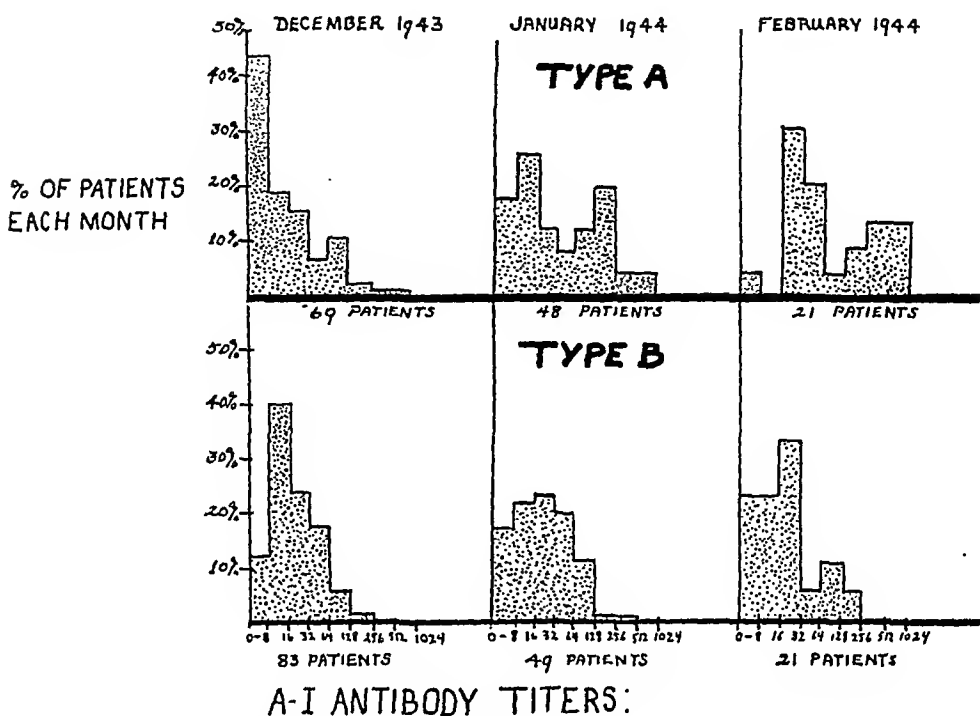
The highest incidence of cases which could be typed occurred during the last days of December, 1943 (Table 1). This was the period during which the epidemic reached its peak in this region. Since there is great individual variation in the so-called "base line" level of A-I antibody of "normal" individuals ($1/4$ to $1/1028$), it is impossible to determine evidence of infection in a patient from a single specimen. However, when the "base line" levels are adjusted on the basis of overlapping known positive sera, to account for variation in reagents due to tests being done on different days, a very definite trend is



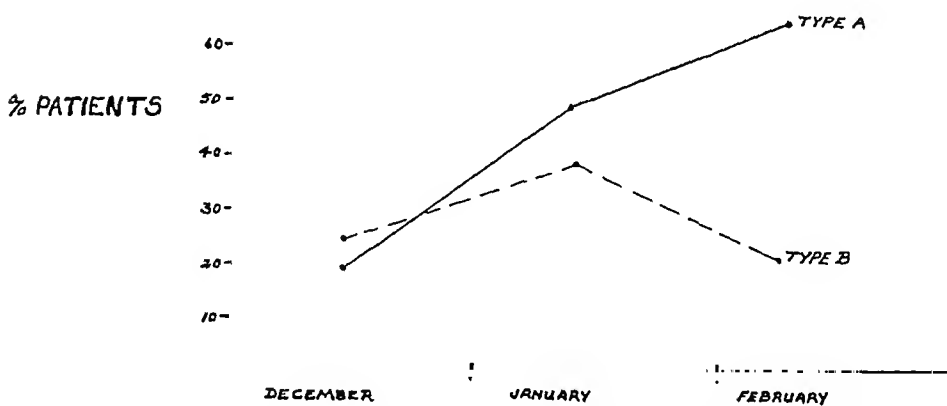
GRAPH 1.—Development of agglutination-inhibition (A-I) antibody for influenza Type A (in 9 patients).

noted as the epidemic subsided. In Graph 2 sera from patients in the acute stages of illness are grouped on the basis of adjusted levels of A-I antibody to influenza Types A and B. These sera were all collected during December, 1943, January and February, 1944. Type A titers are shown for 138 patients and Type B for 153. The smaller number in the former group is due to the fact that in some instances there were no satisfactory overlapping Type A sera. Consequently some of the early determinations could not be adjusted to the sensitivity of those done in later weeks. Although the number of specimens in the third period is considerably smaller, it is apparent that as the influenza epidemic subsided there was a tendency for the A-I antibody level for Type A influenza to rise, while that for Type B remained

essentially unchanged (Graph 3). During these later weeks the laboratory confirmations of influenza were very few.



GRAPH 2.—Effect of Type A influenza epidemic on agglutination-inhibition antibody levels of acute sera.



GRAPH 3.—Per cent of patients each month whose acute sera had corrected A-I titers for influenza Types A and B of 1 to 64 or above.

Discussion. The A-I antibody determination has a number of distinct advantages over the several other methods now available for measuring antibody changes associated with convalescence from influenza. Although no 2 of these tests give entirely concordant results, the A-I antibody more closely parallels the neutralizing antibody than does the antibody detected by the complement-fixation technique.² Per-

formance of this test is also much simpler than is a complement fixation, *in vivo* mouse or egg neutralization. It can be done by any trained laboratory technician. Since guinea pig or human "O" cells may be substituted for chicken cells,¹¹ all the materials necessary for its performance are available in most clinical laboratories, except for the virus. This might be furnished by large central laboratories since the agglutinating ability of the fluid containing virus has been shown to be stable at ice-box temperature for several months.¹ Consequently the laboratory confirmation of a clinical diagnosis of influenza may easily be made routine.

It is appreciated that there are difficulties associated with the test due to variations in cells, virus and human "base line" levels.⁶ Testing both acute and convalescent specimens at the same time avoids many of these. Using the known positive serum in an overlapping manner makes possible an estimation of the relative sensitivity of the test on different days so that comparative studies may be made.

The technique used in this laboratory is not original, but is especially adapted to the facilities of a clinical laboratory. The reading of type of sediment rather than density of supernatant is more practicable in laboratories where a photoelectric densitometer is rarely available.⁷ The use of 8 "agglutinating units" of virus permits easier reading of end-points, though it may decrease somewhat the sensitivity of the test. The small volumes of each reagent which go into the test make for a saving of materials without any appreciable decrease in accuracy. The use of a live virus does not present any great danger as the likelihood of accidental laboratory infection with these "derivative" strains³ is slight.

The importance of proper spacing of specimens is apparent when the incidence of 41% positive reactors obtained when all specimens submitted are compared with the 62% resulting when only those with a satisfactory interval are taken. It would appear that if the first specimen of blood is drawn when a patient is first seen and the second at least 1 week later, the greater percentage of A-I antibody rises would be detected.

The failure of 38% of the influenza convalescents, with satisfactorily spaced specimens, to show evidence of a rise in antibody to either Type A or Type B influenza is of interest. Although a few of these individuals had such relatively high initial antibody levels that slight rises might not have been easily detected, the majority did not. They may represent individuals who have an especially high threshold for producing A-I antibody, or instances of an etiologically different, but influenza-like disease. The one man who developed an increase in A-I antibody to both Type A and Type B influenza virus suggests either a double infection or more likely an anamnestic reaction with Type B antibody. No instances of Type B infection alone were detected in the group.

From an epidemiologic point of view the cases studied were rather unique. They all occurred in previously healthy young men of military age. The greater proportion of cases came from a post which received

men newly inducted from civilian life in that area. They probably reflected the situation in the surrounding civilian community. The next largest group were aviation cadets who had been in the Army for a much longer time. No striking difference was apparent in the response of these 2 groups to the disease. The highest percentage of positive reactors occurred during the 3 weeks at the peak of the epidemic.

The sera represented in Graphs 2 and 3 reflect the influenza agglutination-inhibition (A-I) antibody status of a group of soldiers at the onset of the illness responsible for hospitalization. Most of these patients had probably been exposed to the epidemic of Type A influenza during December and early January. It is therefore significant that their "base line" levels for Type A influenza A-I antibody tended to rise as the epidemic subsided, while those for Type B remained unchanged.

Summary. 1. An epidemic of influenza in several army installations was studied by using an influenza Agglutination-Inhibition (A-I) test.

2. The technique of the test which is modified for use in larger hospital laboratories without special equipment or personnel is presented.

3. One hundred and nineteen clinically typical patients were studied. Of these, 49 (41%) were found to have developed a rise in antibodies to influenza Type A and one to Type B as well.

4. The importance of proper spacing of acute and follow-up sera is shown. The incidence of positive reactors rose to 62% when only those patients from whom a first specimen was taken within 5 days of onset and a second after an interval of at least 5 days were considered.

5. The highest percentage of positive reactors occurred at the height of the epidemic. As the epidemic subsided, the average "base line" level of A-I antibody for Type A among sera submitted for study tended to rise.

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EXPERIMENTAL CHRONIC CARBON MONOXIDE POISONING OF DOGS*

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THE existence of a definite state which may be characterized as chronic carbon monoxide poisoning has not been established. One view of the situation has been summarized by Drinker⁶ as follows: "There can be no doubt that when people breathe small amounts of carbon monoxide daily over weeks and months of time they may suffer ill-health. But the degree of ill-health is variable. . . ." The clinical signs and symptoms of chronic carbon monoxide (CO) poisoning reported in the literature are unfortunately indefinite and uncharacteristic. A further difficulty in evaluating the above quoted statement arises in determining what is actually meant by "small amounts." Bulletin 3 of the U. S. Department of Labor (1941) sets the limit of safe concentration of CO in air in industrial plants at 0.01 vol. % (100 p.p.m.), based upon the report of Bowditch et al.⁴ These values should not be used without reservation. It is well known that occasional short periods of seriously increased gas concentration are hard to avoid in industry and often pass unobserved unless continuous records are kept. If this occurs, the situation changes at once from chronic mild CO intoxication into the range of repeated acute poisoning. A second complication in the problem lies in the evident fact that we are interested primarily in the quantity of CO in the body (measured in per cent of carbon monoxide hemoglobin, [HbCO]) and only secondarily in the amount available in the atmosphere. The actual amount of CO combined with hemoglobin is given only in a few publications, and has been found to vary greatly, even in the same garage.¹¹ Workers may move from regions of extreme exposure to places with low CO concentration. Examinations by Killick¹⁰ have suggested that an individual exposed continually for some months to the same CO concentration in air may, supposedly by adaptation, show a gradual decrease in the percentage of COHb. Hence, safety limits given in terms of CO concentration in air give only an approximate and perhaps unreliable idea of the toxicity relationships of the gas in the body.

The above value of 0.01 vol. % CO in air leads theoretically in man to approximately 16% COHb (calculated, using the value of 210^{13} for K in the equation $K = \frac{[\text{HbCO}]}{[\text{HbO}_2] \cdot p[\text{CO}]}$). By agreement of the Safety Engineers of the U.S.A.,² the upper permissible limit is set at 20% HbCO. These data are based on Haldane's recom-

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Pennsylvania.

mendation to the London Underground Railways in 1897.⁹ One attempt only, so far as we know, has been made to study experimentally whether these figures are innocuous for exposures of months under conditions which actually occur in industry. The results of this study by Suepfle, Hofmann and May¹⁴ are equivocal.

It seemed of special interest in these times of industrial man-power shortage and in view of the fact that there are situations in the Army where routine exposure to sufficient CO occurs to allow formation of 20% HbCO to make a careful study of the effects of chronic exposure to comparable amounts of carbon monoxide. Dogs were chosen as the experimental animals, as continuous exposure over long periods was desired and since in this species also exposure to 0.01 vol. % CO leads to approximately 20% HbCO.

Technique. Six dogs were exposed for 11 weeks, from April 27 to July 13, 6 days a week, with a mean period of exposure of $5\frac{3}{4}$ hours per day, to an atmosphere of approximately 0.01 vol. % CO in the air. A seventh dog was later added to the group so as to observe the effect of the same amount of CO upon an animal whose heart had been damaged, 1 year prior to the present experiment, by means of ligation of the posterior coronary artery. This animal was exposed for 18 days only, and sacrificed 3 months later.

CO Chamber. A controlled flow of compressed air was fed into the chamber to which an initial single amount of pure CO was added. Subsequently a constant amount of 15 mg. pure CO per minute was fed into the air stream with the help of a motor-driven pump. The actual air concentration in the chamber was measured hourly by means of the CO determinator of the Mine Safety Appliance Company (MSA). The MSA apparatus was controlled by use of the iodine pentoxide method and calibrated with the help of gas mixtures of known concentration. Blood of at least 3 dogs within the chamber was withdrawn at the end of the daily exposure and the HbCO content as well as total pigment determined.

The mean (M) of all CO determinations in the air showed that the concentration of the gas was maintained at 0.0096 ± 0.00065 (SD) vol. %. The standard error (SE) of the mean was less than $\frac{1}{10}$ of the mean. The mean of all HbCO determinations in the 6 animals after daily exposure was 20.1 ± 1.1 % (SD), with an SE_M of ± 0.15 . The mean difference of the HbCO determinations from dog to dog on each single day was 1.1%.

Determination of HbCO and Total Hb. HbCO and total pigment were determined spectrophotometrically. The analyses were upon the blood samples diluted 1 to 100 with water. For a description of the spectrophotometric technique, readers are referred to Drabkin and Austin.⁵ In our hands the spectrophotometry has been found to have advantages of accuracy and directness over gasometric methods in determination particularly of mixtures of pigments.³ Special details in the technique as applied to mixtures of HbO₂ and HbCO will be presented elsewhere.

The dogs used in the study were kept long enough in our kennels to convince us of their freedom from acute diseases, especially distemper. None of the dogs showed any sign of disease during or after the experiment.

Results. The condition of all the animals appeared excellent during the whole experimental period.

Temperature, pulse and respiration of all the dogs were taken before the daily exposure and in some at the end of the afternoon, and did not vary beyond usual normal limits. The body weight increased in most of the animals during the first weeks of the experiment and remained stable thereafter. The dietary ration was a mixture of

natural foodstuffs, presumably complete in all essentials. At the end of the experimental period all the animals appeared well nourished. All dogs were of friendly *disposition* at the beginning of the experiment and remained so throughout the whole period. They did not become unduly excited or quiet at the end of the single day of exposure nor at the end of the whole experiment. Even temperatures up to 102° F. in the chambers had no apparent effect, except in 1 dog, made somewhat ill for 1 or 2 days.

Electrocardiograms obtained from the dogs showed changes in the 2nd week of the experiment in 1 animal, and in the 10th week in another. These findings are discussed in detail in a separate paper (Ehrich, Bellet and Lewey⁷). They were interpreted as evidence of permanent myocardial damage. The electrocardiographic changes persisted until the animals were sacrificed 3 months after termination of the experiment. At necropsy the hearts of the 4 dogs which were available for examination showed degenerative changes of individual muscle fibers. A close correlation was found between the electrocardiographic and the morphologic changes.

Periodic *neurologic examination* of all animals revealed almost negligible clinical signs. In 1 dog the pupillary reaction to light decreased, in another the knee jerks became more active, the hopping reaction became poor in 2 dogs, the placing in 3 and jumping in 1 animal. Walking on the fore- or hindlegs when the opposite extremities were supported became difficult or impossible in 4 animals. The dogs showed a tendency to stand and walk on a broad basis, stiff and slightly atactic. No changes were seen in the electroencephalogram or on the part of the peripheral nerves.

The HbCO of the 6 dogs was determined at different times in the morning before the beginning of the exposure, after having been gassed the previous day for 7 hours each and having reached 20% HbCO. In none of the animals could any HbCO be detected. This would appear to support Drinker's opinion that the average values of 2.11% HbCO found by Farmer and Crittenden⁸ in workers 16 hours after exposure were the consequence of smoking on the way to work rather than of delayed elimination.

Morphologic Examination of the Nervous System. The central nervous system of 5 of the 6 dogs exposed to 0.01 vol. % CO in air for a period of 11 weeks, 6 days a week, with a mean exposure of 5½ hours per day, leading to not more than 20% HbCO in the blood at any time, showed distinct histopathologic changes 3 months after termination of the exposure. These changes differed quantitatively from those found in acute CO intoxication, but were qualitatively of the same type and showed the same predilection for certain regions of the brain.

No alterations were found in the *peripheral nerves*.

All animals showed some indication of *cortical damage* of varying type. Figure 1 illustrates a typical wedge-shaped infarct within which the nerve cells of the external granular and pyramidal layers are sclerosed, pyknotic and shrunken. In other instances, the degenerations within the cortex are so diffuse that a dense glia carpet in the

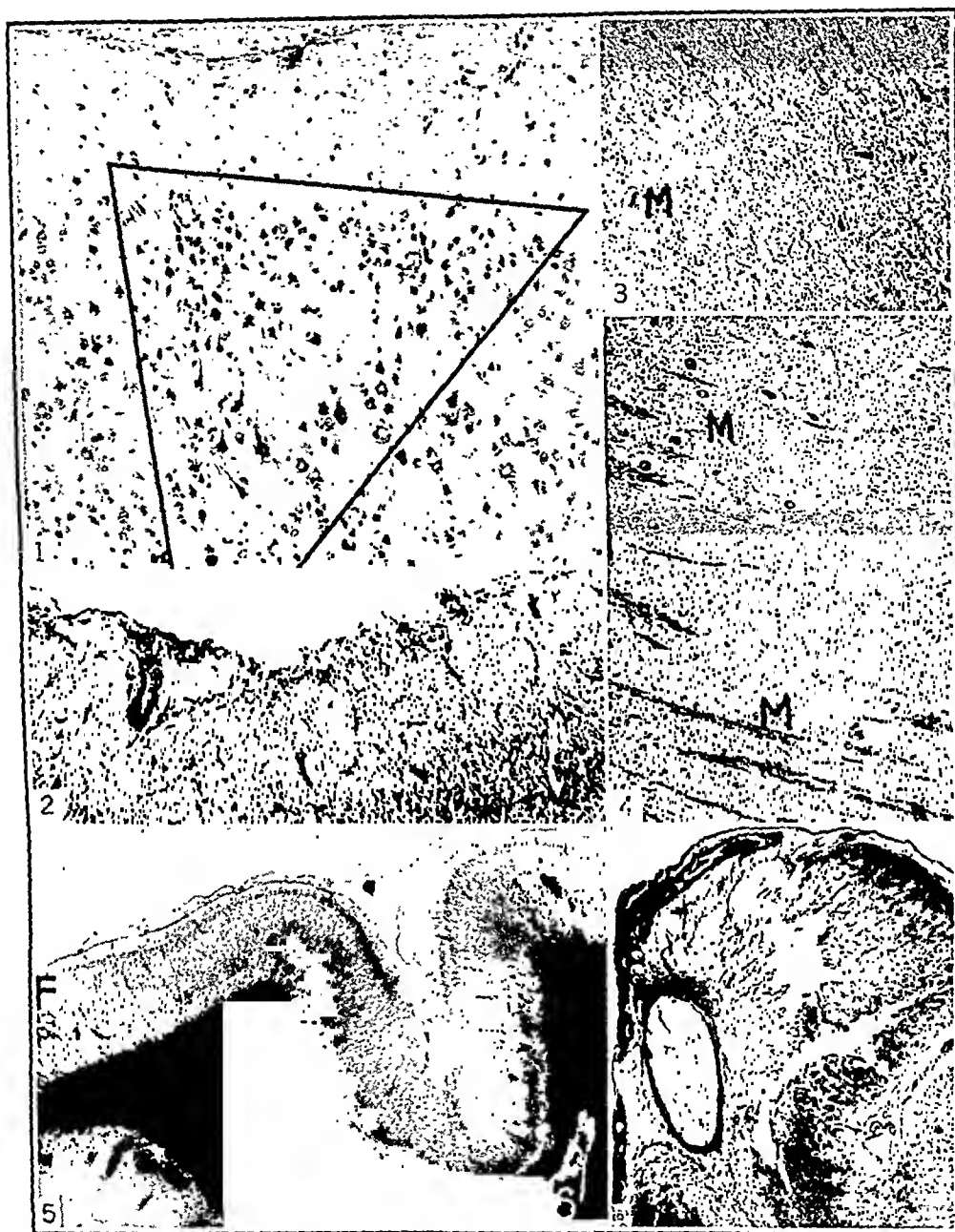


FIG. 1.—Wedge-shaped focus in the cortex in which the cells of the second to fourth layer are pyknotic and shrunken. (321.) (Cresylviolet, $\times 120$.)

FIG. 2.—Dense layer of marginal glia fibers formed on one side of the calcarine fissure. (749.) (Phosphotungstic acid, $\times 150$.)

FIG. 3.—Minute foci of necrosis (mottling) in the cortex (M). (737.) (Phosphotungstic acid, $\times 70$.)

FIG. 4.—Minute foci of necrosis (mottling) in the lateral thalamic nucleus (M). (749.) (Phosphotungstic acid, $\times 70$.)

FIG. 5.—Cavity formation in the cortex (F) and in the white matter (S) of F₃. (321.) (Weigert, $\times 10$.)

FIG. 6.—Large cyst formation within necrotic area of frontal lobe. (737.) The cyst is walled off by a connective tissue capsule which is surrounded by a glia capsule. (Laidlaw's silver impregnation, $\times 30$.)

superficial cortical layers is the sole sign of cortical disintegration (Fig. 2). In 1 dog a spongy degeneration of all layers of a convolution resembles closely the appearance of the cortex as seen in severe anoxia through occlusion of the pial vessels.

The mildest form of this "anoxic necrosis" is expressed in form of "mottling" of the cortex (Fig. 3) or of the lateral thalamic nucleus (Fig. 4), i. e., minute foci of disintegration in which myelin, axis cylinders and ground substance alike have broken down and are so completely cleaned out that not even a scar has been formed. Small cavities are the only indication of the degeneration of the parenchyma. In the dog with preceding cardiac operation (321), stasis in the cortical blood-vessels clearly played a dominant rôle, producing grapelike cortical cavities (Fig. 5), whereas the large subcortical foci are probably true necroses rather than the consequence of vascular obliteration.

Occasionally both the superficial vascular system of the pia and the deep system of the large ascending arteries of the *circulus arteriosus* seemed to be involved. In these instances a whole convolution or a greater part of it became necrotic to the degree of forming large cysts (Fig. 6). Their anoxic origin is still evident from the fact that the scar in the white matter surrounding the cyst is purely gliotic, whereas the immediate capsule of the cyst as well as the repair of the cortical necrosis are of mesodermal nature.

The involvement of the long arteries of the white matter is clearly manifest in the large and small foci of softening in the *white matter*, prominently in the occipital lobes (Figs. 7 and 8) and in the dissolution of the U fibers (Figs. 9 and 10), which as a rule belong to the most resistant structures of the brain but were reported as involved in acute CO poisoning by Meyer.¹² In a milder form of vascular impairment patches of perivascular gliosis in the white matter (Fig. 11) or small softenings in the nuclei of the brain stem (Fig. 12) are indicative of the damage produced.

Of most significance are the changes in the *basal ganglia* which, though of minor severity, are more frequent in these chronic than in acutely poisoned animals which we have studied. Here again all gradations are seen. Demyelination of the fibers in the capsula externa, the putamen, the external and internal medullary bundles, as well as of the thick fibers in the globus pallidus proper seem to characterize the earliest signs (Figs. 13 and 14). Loss of axis cylinders in the same bundles suggests a more advanced process (Figs. 15 and 16). In 1 animal a circumscribed but complete softening in the most medial and anterior part of the globus pallidus was found along the course of an artery, the walls of which were necrotic (Fig. 17). The focus is so neatly cleaned out that it may be inferred that it had appeared several weeks prior to death.

Discussion. The clinical signs in 7 dogs which had breathed an atmosphere of 0.01 vol. % CO for 5½ hours a day, 6 days a week, over a period of approximately 3 months were not impressive. But they were, nevertheless, slightly less vague than symptoms and signs de-

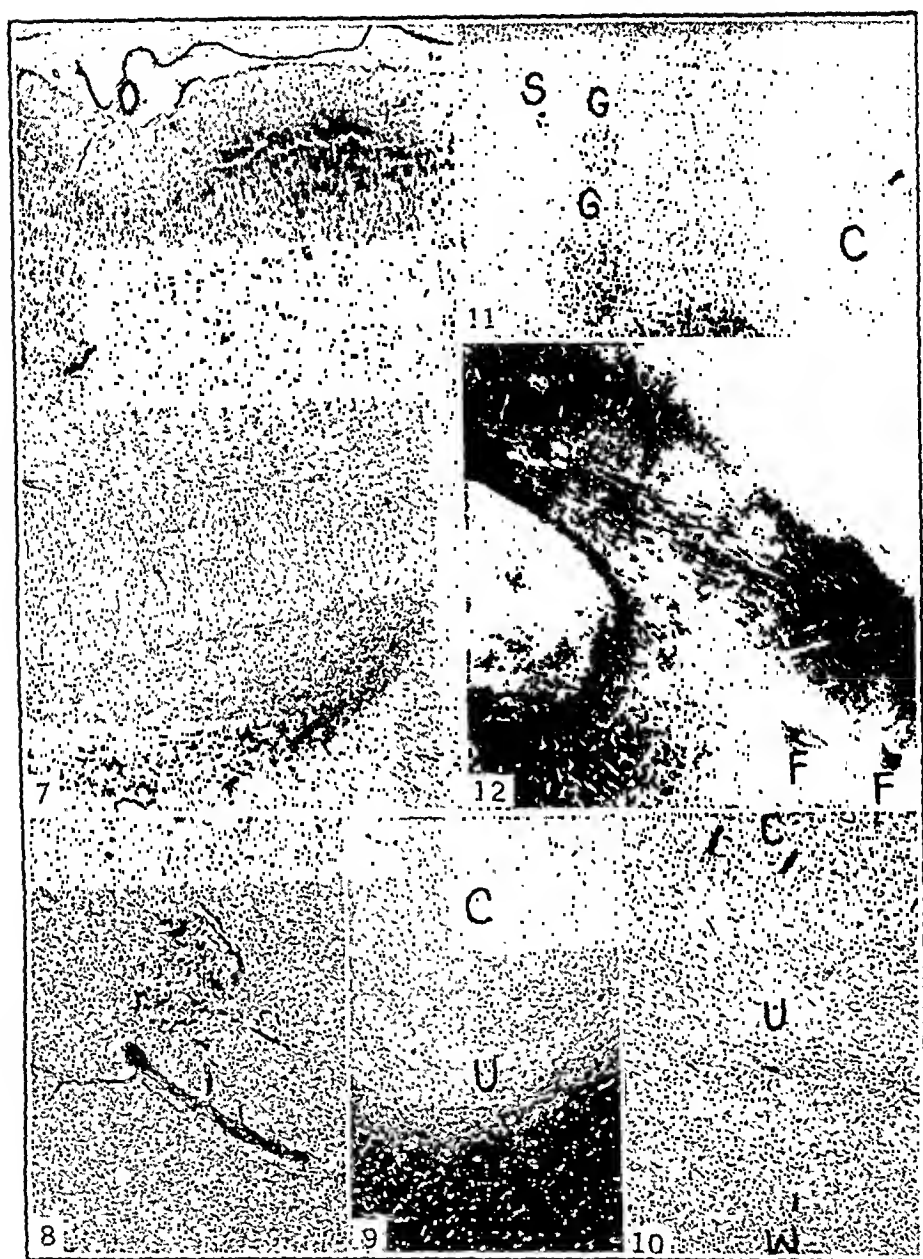


FIG. 7.—Large softening with reparatory sprouting of capillaries in the occipital lobe. (749.) (Cresylviolet, $\times 30$.)

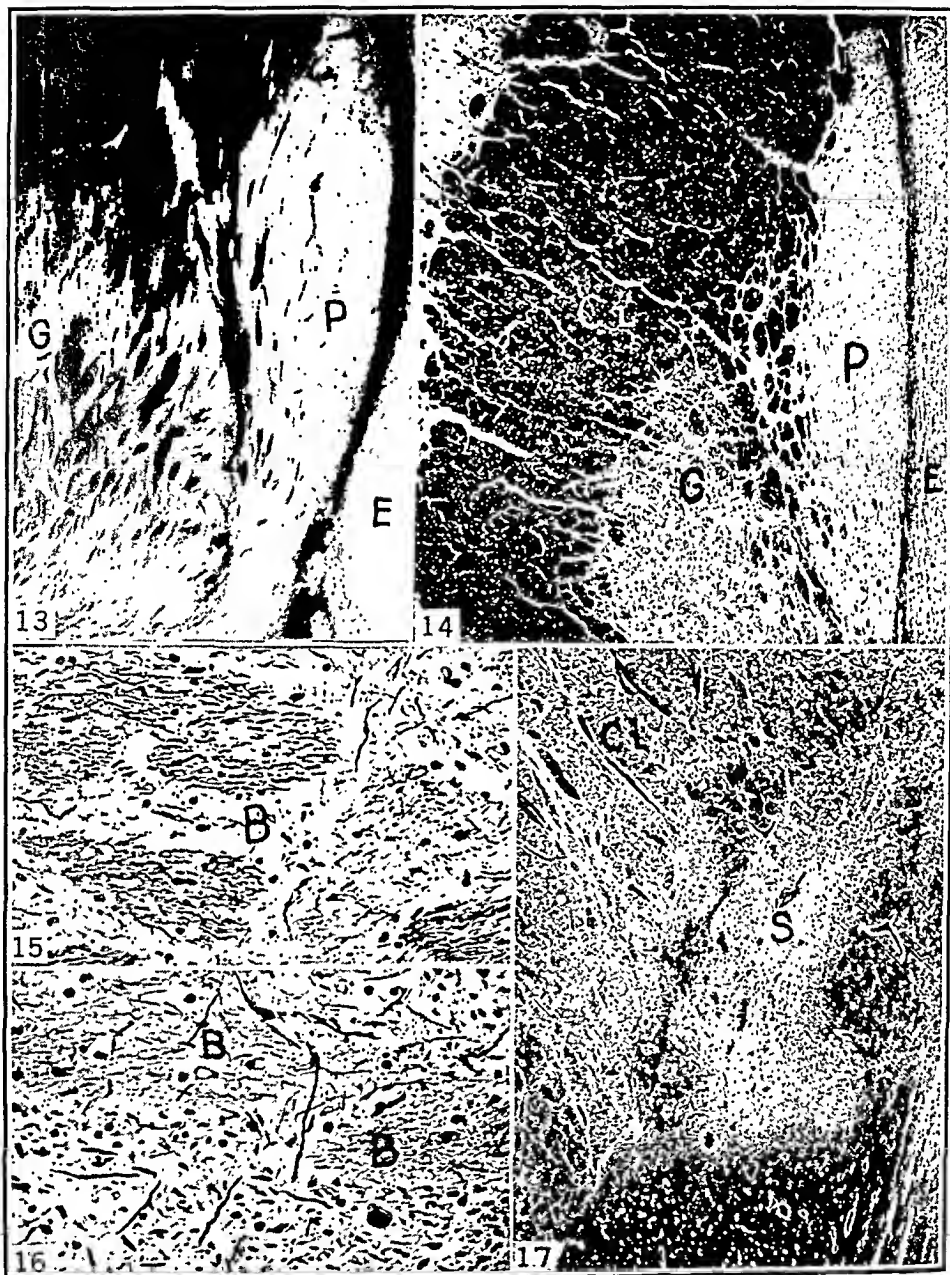
FIG. 8.—Small focus of disintegration with connective tissue scar in connection with proliferated blood-vessel in occipital lobe. (321.) (Laidlaw's silver impregnation, $\times 70$.)

FIG. 9.—Loss of U fibers (U) below cortex (C). (739.) (Phosphotungstic acid, $\times 30$.)

FIG. 10.—Loss of U fibers under higher power (U). Cortex (C). White matter (W). (739.) (Bodian axis cylinder staining, $\times 70$.)

FIG. 11.—Softening (S) and foci of perivascular gliosis (G) in the occipital lobe underlying the cortex (C). (737.) (Phosphotungstic acid, $\times 30$.)

FIG. 12.—Foci of softening and cavity formation (F) in the corpus geniculatum medialis and the lateral lemniscus. (321.) (Weigert, $\times 10$.)



FIGS. 13 and 14.—Putamen (*P*) and globus pallidus (*G*) in the same magnification ($\times 20$). Figure 13, a normal control dog; Figure 14, chronic CO_2 dog (737) *Ci*, capsula int. *E*, capsula externa. The loss of medullated fibers in putamen, globus pallidus and laminae medullares is evident. (Weigert: myelin sheaths.)

FIGS. 15 and 16.—Shows cells and fiber bundles of the globus pallidus with axis cylinder impregnation. Figure 15, a normal control dog; Figure 16, a chronic CO dog (739). Figure 15 shows large nerve cells and dense bundles of axis cylinders (*B*), whereas the nerve cells in Figure 16 are shrunken and the bundles (*B*) void of axis cylinders except for one in the right lower corner. (Bodian axis cylinder impregnation, $\times 330$.)

FIG. 17.—Large focus of softening along necrotic blood-vessel in the most anterior and medial part of the globus pallidus. *S*, softening; *Ci*, internal capsule. (746.) (Laidlaw's silver impregnation, $\times 30$.)

scribed as characteristic of chronic CO poisoning in man. It may be worthwhile to check whether the anomalies of gait and posture, which represented the only constant findings in these dogs, may also be found in man after chronic exposure to CO.

The disposition of all our dogs remained friendly. Suepfle *et al.*¹⁴ observed that their dogs became irritable and easily frightened towards the end of their experiment of 13 weeks' duration. This psychic reaction disappeared after termination of the intoxication. Hence, workers came to the conclusion that the exposure of dogs to 0.01 vol. % CO, even over several months, failed to produce any clinical signs while 0.02 vol. % represented for dogs the limit of tolerability because of the described psychic changes. However, Suepfle and colleagues report that exposure to 0.01 vol. % CO for 5½ to 6 hours daily led in their dogs to only 7% HbCO and exposure to 0.02 vol. % CO to only 13% HbCO. These findings appear incomprehensible to us, since our animals invariably reached values of 20% HbCO in exposure to 0.01 vol. % CO. The results of Suepfle *et al.* are therefore difficult to interpret.

The clinical findings in our dogs were too uncharacteristic to be of any value were they not confirmed by mild but definite histologic changes in the hemispheres, basal ganglia and the stem of the brain. There is no doubt that type and localization of the histologic alterations in the brain of the chronically intoxicated animals, including their strange predilection for the anterior part of the globus pallidus are identical qualitatively with those seen in acute CO poisoning. The difference between the histologic changes in acute and chronic CO poisoning appears to be purely quantitative. The chronic foci are more scattered, the lesions smaller, and the axis cylinders in them often preserved.

The presence of the histologic changes which have been described in the brain of all 5 dogs available for histologic examination and their absence in all controls, kept upon the same diet and under the same living conditions, leaves little doubt that they have to be considered as due to chronic CO intoxication.

It should not be inferred that similar changes need be expected in the human brain under the same conditions.

No data concerning histologic examinations of the nervous system in chronic CO poisoning of man or animals could be found in the literature. However, one may speculate that similar changes might be detected also in man if the brains of individuals who had survived subacute or chronic CO poisoning without having shown marked or persistent clinical signs were available for examination. It is well known that at necropsy numerous cortical and subcortical foci may be found in man after lethal subacute CO intoxications, although the clinical signs and symptoms had been vague and inconclusive. In addition, Alexander¹ has demonstrated that extensive thromboses of both globi pallidi may not be followed by their clinical equivalent, Parkinsonism, until 15 years after intoxication with carbon monoxide.

Our dogs showed the same value of 20% HbCO after 13 weeks of

exposure as that found after the 1st day of gassing. Thus, there was no evidence of acclimatization to CO in our experiments, as has been reported.^{9,10}

Finally, Drinker's⁶ question as to the response of the damaged heart to CO may be answered tentatively. The animal in which the posterior coronary artery had been ligated 1 year prior to the chronic CO intoxication showed by far the earliest and severest pathologic changes in both the heart and brain. We do not wish to overemphasize the outcome of this experiment upon one animal, but the result is suggestive.

The implication of the present findings with respect to chronic CO intoxication in man is uncertain, but one fact seems to stand out, namely that 0.01 vol. % CO leading to 20% HbCO is not innocuous for the heart and central nervous system of dogs.

Summary. 1. Dogs, exposed for 5½ hours per day, 6 days a week, over 11 weeks, to an atmosphere containing 0.01 vol. % CO, and reaching daily $20.1 \pm 1.1\%$ HbCO, showed a consistent disturbance of postural and position reflexes, and of gait.

2. Some of them showed a pathologic electrocardiogram, characteristic of anoxia, and necrosis of single heart muscle fibers.

3. Their central nervous systems showed, 3 months after termination of the experiment, histologic changes in the cortex and white matter of the cerebral hemispheres, in the globus pallidus and the brain stem. These alterations corresponded in type and localization to those found in acute CO poisoning, but were smaller, more scattered and less destructive. They followed in their arrangement the course of blood-vessels, the walls of which were damaged only occasionally.

4. One dog, in which the posterior coronary artery had been ligated 1 year prior to the exposure for a period of only 18 days to CO, showed the earliest and severest cardiac and cerebral changes of all animals observed. This result suggests that an inadequate functioning heart increases the general risk in CO poisoning, and may be responsible for a higher degree of brain damage.

5. Our findings indicate that chronic CO intoxication may occur in dogs at CO concentrations which have been regarded as being within the safety limits for man.

6. These experiments do not permit any conclusions as to the potential reactions of the human body to the same conditions.

We wish to express our appreciation to Lt. Col. Theodore F. Hatch, Sn.C., of the Department of Industrial Hygiene, for his technical advice in the arrangement of the experiments, to Dr. William Ehrich of the Department of Pathology and Dr. S. Bellet of the Cardiac Department of the Hospital of the University of Pennsylvania for their coöperation, and to Mr. Richard Faber, now a senior in the School of Veterinary Medicine, and Miss H. Lorraine Leidy for valuable technical assistance.

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CARDIAC CHANGES FROM CO POISONING*

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WHILE cerebral lesions from CO poisoning have been repeatedly described, the cardiac changes are not generally recognized. Thus, Drinker¹⁰ has recently stated that there seems to be no definite pathologic evidence of serious cardiac damage in CO intoxications except in the severest degrees of poisoning; in fact, Stearns, Drinker and Shaughnessy³⁰ have reported that even in lethal doses marked changes in the electrocardiogram may be missing. In view of these and similar statements, we wish to present some observations made during an experimental study of CO poisoning in dogs which seem to indicate that the heart is frequently involved in CO poisoning, and that the cardiac changes are more severe than previously realized.

Literature. Cardiac involvement in CO poisoning was first noted by Klebs.²⁰ Clinically, he recorded acceleration, and later irregularity and retardation of the heart beat; anatomically, he observed punctiform and diffuse hemorrhages into the pericardium and endocardium, including the tips of the papillary muscles. In at least 1 case he found fatty dystrophy of the myocardium. The clinical observations of Klebs were confirmed by Zondek,³³ Killick,¹⁹ and others, and subsequent writers added to the picture changes in the electrocardiogram such as alterations of the T waves and the S-T segments as well as the symptoms of stenocardia.^{8,21,24} The anatomic findings of Klebs were amplified by Liebman,²⁵ who seems to have been the first to observe myocardial necrosis in CO poisoning. These findings were

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Pennsylvania. Responsible Investigator: Major F. H. Lewey, M.C., A.U.S.

later corroborated by Herzog,^{16,17} who observed necrosis and fatty dystrophy in the papillary muscle of the mitral valve, in the apex of the heart, and elsewhere in the left chamber in 14 out of 16 patients; while Gey¹¹ found hemorrhages especially in the apex of the papillary muscle of the mitral valve, fatty dystrophy of the myocardium, and occasional circumscribed necroses in 9 out of 19 patients. Similar observations have since been reported by several other writers.^{12,13,31,32}

Although efforts to induce cardiac changes in experimental CO poisoning were not successful in the hands of some investigators,^{25,33} Haggard¹⁵ found in dogs occasional ventricular extrasystoles, inversion of T waves, and heart block; Campbell⁵ in a few animals noted marked fatty dystrophy of the myocardium; and Christ⁷ in rabbits observed negative T waves and broadening and depression of the R-T segment, as well as subendocardial necroses, especially at the base and apex of the left papillary muscle. No hemorrhages were seen in these experiments.

For the sake of completeness, it should be mentioned that some authors claim to have observed extensive capillary thrombosis of the myocardium,² but the evidence presented appears to us insufficient.

Material and Method. All experiments were performed upon stray dogs which were quarantined for a few days to determine their freedom from disease such as distemper. Some experiments represent acute CO intoxication, others chronic poisoning.

In the acute experiments Nos. 238/I, 246, 249, 256, 258, 324, 368, 388, 450, 473 and 615, the animals were allowed to inhale the CO. In some of these, the dogs were connected by a tracheal cannula to a 2-liter rubber bag into which pure O₂ was delivered. The expired air passed through an externally cooled canister filled with soda lime before returning to the bag. Into this closed system freshly prepared CO (96%) was fed in varying quantities and at various intervals. In other experiments of this series a bell-jar was placed over the head of the dog and fixed, by means of a rubber collar, around its neck. Compressed air, the flow of which was controlled by means of a flow-meter and to which 15 cc. of CO per minute were added by a motor driven pump, was fed into the bell-jar and allowed to leave at the collar. In 3 animals of this first series (Nos. 238/I, 368, 388), CO₂ accumulated within the closed system because of an error in technique. Three dogs (Nos. 246, 256, 258) with acute circulatory failure were kept alive by transfusion with about 250 cc. of dog's erythrocytes suspended in an amount of saline solution just sufficient to permit injection.

In a second series of acute experiments (Nos. 198, 233, 238/II, 239, 267) CO was administered by way of intravenous injection of erythrocytes 96% saturated with CO outside the body.

In a series of chronic experiments (Nos. 737, 739, 740, 749) the dogs were exposed in a closed chamber to CO for 5½ hours a day, 6 days a week, over a total period of 11 weeks. The concentration in the chamber was sufficient to obtain about 21% COHb. It amounted to 0.01 vol. % CO, a dose generally regarded as non-toxic.

The dogs Nos. 696, 738, 741, 743, 744 and 745, finally, were placed in a chamber in which the O₂ of the breathing air was reduced to 10 vol. % leading to a partial O₂ pressure in the blood similar to that of 21% COHb. This was continued for 4½ hours a day, 6 days a week, over a total period of 11 weeks.

Two of the acutely poisoned dogs died at the end of the experiment, obviously from the experimental procedure (Nos. 238/I and 239). Two others died after 4 days because of gas infection (No. 256) and confluent broncho-

pneumonia (No. 388). The remaining acute animals were sacrificed at intervals from 4 days to 2 months, some by bleeding, others by air embolism.

The chronic animals were allowed to live for 6 to 7 months after the onset of the experiments, *i. e.*, 3 months after termination of the CO poisoning or the O₂ deficiency. Most of these animals were killed by bleeding.

The organs studied include brain, heart, lungs, liver, kidneys, spleen, intestine, adrenals and lymph nodes. The findings of the brain will be presented elsewhere (by F. H. L.) and therefore will not be discussed here.

Results. General Observations. Ten of our animals showed granulomata due to parasites in various organs including lymph nodes, kidneys, lungs, liver, spleen and pancreas; but only 2 showed granulomata in the heart (Nos. 368 and 745). Two dogs harbored tapeworms in their intestines; 2 had Gandy-Gamma bodies in their spleen, and 3 foci of old pyelonephritis and calcified casts in their kidneys. Only 1 animal showed indication of preëxisting more severe disease, namely marked prominence of the juxta-glomerular apparatus of the kidneys as well as hypertrophy of the heart (No. 368).

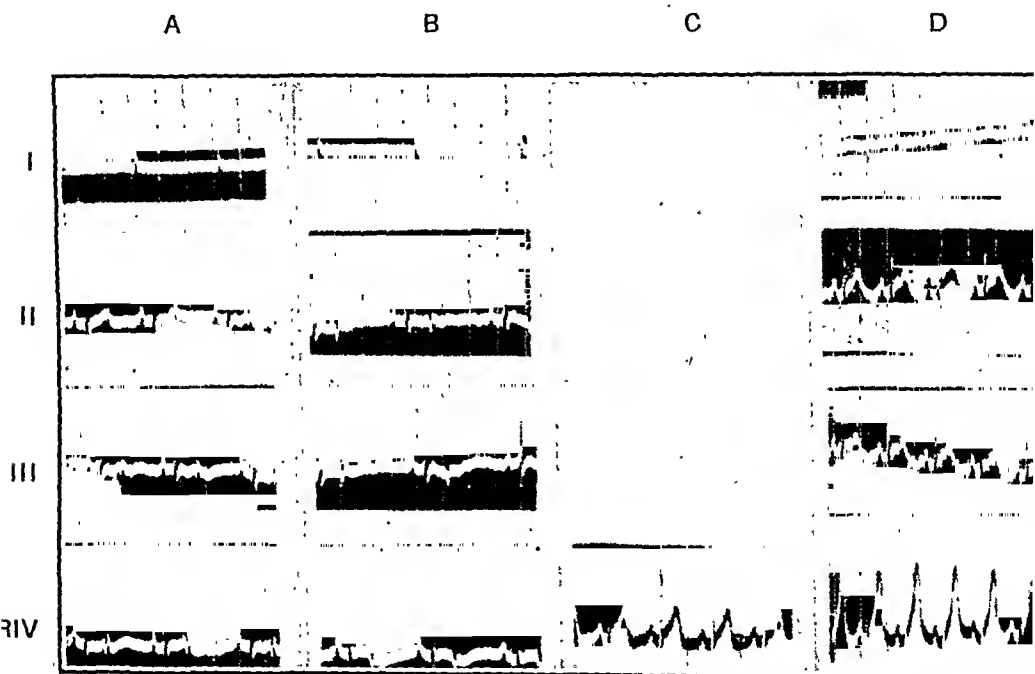


FIG. 1.—Electrocardiograms of Dog 473. Acute experiment, CO inhalation. (A) Control 7 P.M. Leads I, II, III and CRIV; (B) 8:25 P.M. 40% COHb. Note the sharp T wave inversion in Leads II and III and elevation of T in CR 4 with inverted T waves and sharp downward dip. (C) Lead CRIV, 8:51 P.M. 67.5% COHb. Note upright T wave with slight RT elevation. (D) 9:35 P.M. 79.5% COHb. Note RT elevation in Lead II, tall T wave in CRIV and presence of tachycardia. Ventricular rate is 200 per minute.

Electrocardiographic Observations. The earliest electrocardiographic change observed in an acute experiment (No. 473) at a COHb level between 40 and 50% COHb consisted in a decrease of the T wave (Fig. 1). The T wave became diphasic and sometimes negative at 70%, and permanently negative when COHb increased from 70 to

75%. After respiration had stopped, and artificial respiration and blood transfusion were administered, the electrocardiogram showed a 2:1 atrioventricular block and a negative T wave as well as an elevation of the R-T segment. The block disappeared within 24 hours, but the T wave remained negative until the animal was sacrificed 4 days after the experiment.

In the 2 animals of our second series which were transfused with erythrocytes saturated with CO, and which were studied electrocardiographically (Nos. 238/II and 239), the sole change in the electrocardiogram consisted of an inversion of the T wave. The highest COHb level obtained in Dog 238/II was 72 to 74.4% for 15 minutes; in Dog 239 it exceeded 75% for 45 minutes and reached 84.4 to 85.6% for 10 minutes. However, the number of erythrocytes in the circulation was doubled in Dog 238/II and increased 6.6 times in Dog 239, which means that the oxygen combining power at this time was considerably higher than would appear from these percentages. In Dog 238/II, for instance, the CO-free hemoglobin did not amount to 25.6 to 28% of the original quantity, but, since the number of erythrocytes was doubled by transfusion, this dog had more than 50% of the original amount of CO-free hemoglobin. Similarly, Dog 239 had as much as 95% of the original amount. Obviously, then, the oxygen combining power was reduced by only about 50% in 1 dog and not more than 5% in the other.

In the chronic experiments, no electrocardiographic changes were observed during the 1st week of the experiment (Nos. 737, 738, 739, 740, 741, 744, 745). After the 2nd week the T wave became negative in 1 CO poisoned dog (No. 739) and in 1 animal under decreased O₂ tension (No. 745) while another of this group (No. 738) developed an elevation of the R-T segment. At the 10th week the CO dog (No. 737), previously negative, developed an inverted cone-shaped T wave. These changes continued unabated until the animals were sacrificed 3 months after termination of the experiment.

Morphologic Observations. Table 1 lists the average *weights of the hearts* and other organs often involved in circulatory disturbances in all of our animals except Nos. 256 and 388, which died from intercurrent diseases, No. 368 which suffered from cardiorenal disease, and No. 744 of which no body weight was taken at the end of the experiment. The heart weights of the dogs in the chronic CO experiments were slightly greater than those of our non-fatal acute experiments. This is in accord with the observations of Campbell,⁶ who found a considerable increase in heart weight in mice which were exposed to chronic CO poisoning for 9 months. This was explained by an increase in viscosity of the blood owing to the increase in red cells. The increased heart weights which were found in our fatal acute experiments were probably the result of passive congestion.

Concerning the other organs, it can be learned from Table 1 that the lungs were enlarged in the 2 fatal experiments, and this increase amounted to 4 times the normal weight in No. 239, the blood volume of which had been augmented 6.6 times. The kidneys were enlarged

in our non-fatal transfusion experiments as well as in both fatal experiments, while the spleen was enlarged in the non-fatal transfusion experiments, but not in No. 239. The changes in the fatal inhalation experiments seem to be explained by circulatory failure, while those in the fatal and non-fatal transfusion experiments appeared to be partly caused by the introduction of the large quantities of blood. The failure of enlargement of the spleen in No. 239 was due probably to the early death of this animal, the death occurring at a time when as previously observed¹ the spleen was contracted as a result of acute oxygen want.

TABLE 1.—THE RELATIVE WEIGHTS $\left(\begin{smallmatrix} \text{organ weight, gm.} \\ \text{body weight, kilo} \end{smallmatrix} \right)$ OF HEART, LUNGS, LIVER KIDNEYS AND SPLEEN IN OUR VARIOUS EXPERIMENTS

Non-fatal Experiments						
	No. of dogs	Average weights				
		Heart	Lungs	Liver	Kidneys	Spleen
Inhalation of CO, acute . . .	7	7.85	9.50	32.2	5.20	2.1
Transfusion with COHb, acute	4	7.70	9.70	28.0	6.15	3.6
Inhalation of CO, chronic . .	4	8.70	9.05	30.4	4.40	2.0
O ₂ deficiency, chronic . . .	5	8.20	11.60	31.6	5.10	2.2
Fatal Experiments						
Inhalation of CO, acute . . .	1	8.80	16.10	37.6	7.00	3.3
Transfusion with COHb, acute	1	9.60	40.70	30.4	7.10	2.1

The gross appearance of the hearts was essentially normal in all our chronic experiments and in the non-fatal acute experiments except in No. 473 which was studied electrocardiographically (see page 513) and sacrificed 4 days after the poisoning. In this animal we found extensive subendocardial hemorrhages throughout the left ventricle with special involvement of the papillary muscles. In Nos. 238/I and 239 which died from the experimental procedure the hearts were much dilated and filled with coagulated blood, and in No. 239 gross hemorrhages were present throughout the endocardium of the left ventricle, the papillary muscles being particularly affected. Of the 2 dogs which died from intercurrent diseases, No. 388 showed marked dilatation of the heart with hemorrhages in the papillary muscles of the left ventricle, while No. 256 exhibited no more than acute parenchymatous degeneration.

The microscopic examination of the hearts showed 2 types of alterations, namely, (1) hemorrhages and necroses and (2) what appeared to be degenerative changes of individual muscle fibers. Hemorrhage without necrosis was observed in the 2 acute experiments which terminated fatally at the end of the experimental period (Nos. 238/I and 239). One of these dogs had been poisoned by inhalation, the COHb level exceeding 75% for 3 hours, and 80% for 80 minutes. If no necrosis developed, this was probably due to the fact that the animal expired before anatomic changes could manifest themselves. The other dog (No. 239) had been poisoned by transfusion, the COHb level exceeding 75% for 45 minutes and 84.4% for 10 minutes. But in this animal the blood volume had been increased 6.6 times, that is to

say, the amount of CO-free hemoglobin still equaled about 95% of the original quantity (see page 514). Whether or not necrosis would have developed here, if the animal had lived long enough, is question-

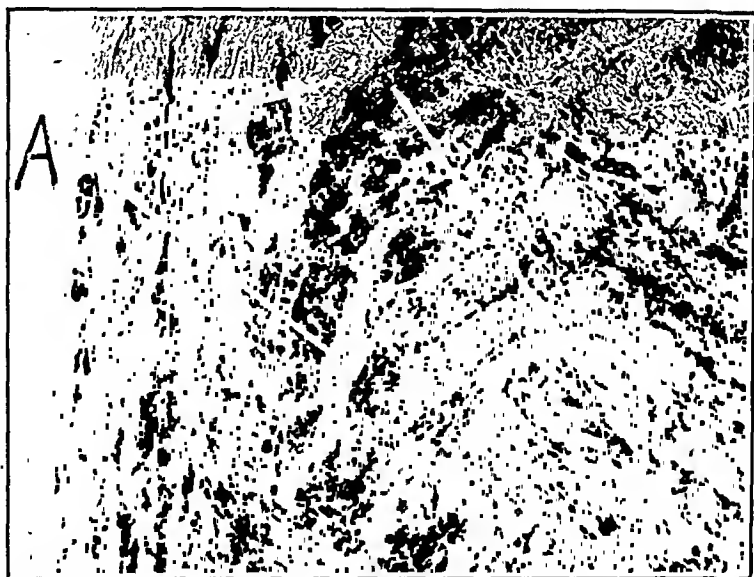


FIG. 2.—Dog 473. Killed 4 days after poisoning by inhalation. Note black areas of extensive subendocardial hemorrhage (A) and necrosis (B). (Mallory stain, $\times 92$.)

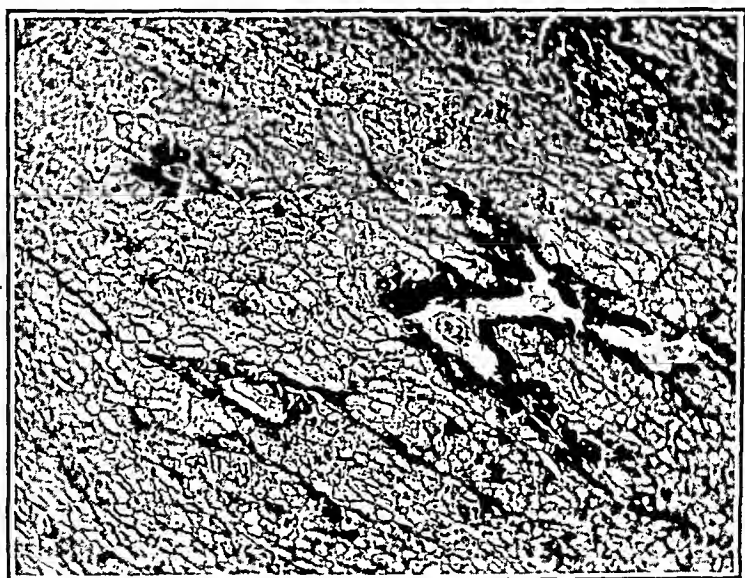


FIG. 3.—Same as Figure 2. Shows acute perivascular necrosis. (Mallory stain, $\times 149$.)

able. It is conceivable that the hemorrhages in this dog were due solely to the enormous quantity of blood which was eventually in circulation.

Hemorrhages as well as necroses were present in CO No. 473 (Figs. 2 and 3) which was sacrificed, and in CO No. 388 (Fig. 4) which died from bronchopneumonia, both 4 days after an acute experiment. *Necroses alone* were found in Nos. 246 (Figs. 5 and 6) sacrificed 7 days after inhalation of CO, and Nos. 743 (Fig. 7) and 745 (Fig. 8) sacrificed 3 months after termination of chronic O₂ deficiency. Nos. 473, 388 and 246 were all poisoned by inhalation, their COHb level exceeding 75% for 1 hour or more. No. 473 was brought up to 76.7%, No. 388 to 82% and No. 246 to 90% COHb.



FIG. 4.—Dog 388. Died 4 days after poisoning by inhalation from confluent bronchopneumonia. Note dark areas of acute myocardial necrosis. (Hematoxylin-eosin, $\times 110$.)

The hemorrhages and necroses were scattered especially through the subendocardial layers of the left ventricle with particular involvement of the papillary muscles (Figs. 2, 5 and 7). Fresh areas of necrosis were deep red in color when stained with hematoxylin-eosin, and purple or blue with Mallory's stain. In a good many places the necroses showed a definitely perivascular arrangement (Figs. 3 and 6). There were no leukocytes present at the time when the hearts were examined, but early organization was observed in No. 388, early calcification in Nos. 246 (Fig. 6) and 745 (Fig. 8) and late calcification in No. 743 (Fig. 7).

Of the 11 dogs which did not develop hemorrhages or necroses from acute poisoning, 7 never reached 75% COHb (Nos. 198, 233, 238/II, 249, 256, 324, 368). The other 4 reached levels from 75 to 84.3%,

but 3 of these remained above 75% for only 15 minutes or less (Nos. 258, 450, 615), while the fourth (No. 267) was kept above 75% for a little over 1 hour; but in this experiment the CO was given by transfusion and there was a marked increase in the number of erythrocytes

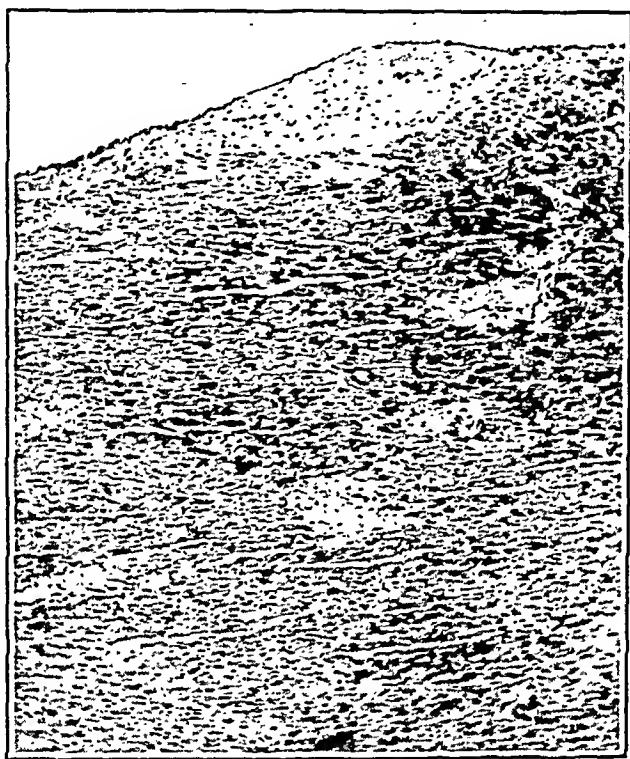


FIG. 5.—Dog 246. Killed 7 days after poisoning by inhalation. Shows extensive necrosis in papillary muscle. (Hematoxylin-eosin, $\times 135$.)



FIG. 6.—Same as Figure 5. Shows dark areas of early calcification of necrosis. (Hematoxylin-eosin, $\times 230$.)

in the circulating blood so that the quantity of CO-free hemoglobin amounted to a greater percentage than that found in the animals which developed necroses.

In 1 of the 2 chronic O₂-deficient animals (No. 745), the necroses seemed to be fairly recent and were probably due to some pathologic



FIG. 7.—Dog 743. Killed about 4 months after period of chronic O₂ deficiency. Shows old calcified necrosis (black) of papillary muscle. (Hematoxylin-eosin, $\times 132$.)



FIG. 8.—Dog 745. Killed about 4 months after period of chronic O₂ deficiency. Shows darker calcified necrosis of papillary muscle. (Hematoxylin-eosin, $\times 132$.)

process during the course of observation; while they appeared old in the other (No. 743) and were possibly due to an episode preceding the experiment. The dog showing recent necroses had had a negative T wave while alive; the other had not been studied electrocardiographically.

The *degenerative changes of individual muscle fibers* which were mentioned above were found in one normal control dog (No. 266) (Fig. 9). Of the experimental animals, Nos. 233, 238/II, 256, 258, 324, 696 and 741 seemed to be free of these changes, and Nos. 198, 267, 368, 615 and 744 were questionably free; but No. 450 which was poisoned by inhalation up to 83.3% COHb was definitely positive, and there were marked degenerative changes (Fig. 10) in the chronic CO animals (Nos. 737, 739, 740, 749) and the chronic O₂-deficient animal No. 738.



FIG. 9.—Dog 266. Control experiment. Longitudinal section. Altered muscle fibers staining bright orange appear black in photo. (Mallory stain, $\times 368$.)

The microscopic appearance of these changes is best studied in Figure 9, representing a longitudinal section. It can be seen that the changed portions of the fibers were narrow and hyaline in appearance; they stained deep red with hematoxylin-eosin, and bright orange with an overdifferentiated Mallory stain; and they were often limited to segments between intercalated disks. The only changes reported in the literature resembling these alterations seem to be those which

Orsos²⁸ described as "vital reactions." However, whether our changes were "vital" or artefacts could not be decided, though it is noteworthy that 3 of these dogs had presented electrocardiographic changes while alive (Nos. 737, 738, 739); 1 had not been studied electrocardiographically (No. 749); and only 1 showed a normal electrocardiogram (No. 740).



FIG. 10.—Dog 739. Cross-section of myocardium. Altered muscle fibers, staining bright orange appear black in photo. (Mallory stain, $\times 138$.)

If we turn now to the *deposition of fat and hemosiderin* which are often found in circulatory disturbances, it may suffice to say that no significant differences in the fat contents were found in the various organs in the various experiments, though the renal tubules and glomeruli contained more fat in the chronic experiments than in the acute ones.

The amount of hemosiderin deposited in the spleen was found to be increased in the transfusion experiments, which seems to be explained satisfactorily by the introduction of so many erythrocytes into the circulation.

Discussion. Our findings in dogs closely resemble those obtained by previous investigators in experimental animals. Exposure to CO was followed first by decrease in amplitude of the T wave, inversion of the T wave, elevation of the R-T segment, and later by atrioventricular dissociation and A-V heart block. The changes in the T wave and R-T segment appeared in acute experiments at a COHb level of 40%, while heart block was observed only when the COHb level exceeded 75%. After a certain length of time, all animals maintained at this level collapsed, and there was evidence of respiratory failure and cerebral damage. These observations were confirmed in subsequent experiments which will be reported elsewhere.

In chronic experiments T-wave changes appeared after the 1st week of exposure to CO in 2 animals which manifested a COHb concentration of 21%.

Morphologic examination of the hearts revealed hemorrhages and necroses in the myocardium of all animals the COHb level of which exceeded 75% for 1 hour or longer; while those which remained beneath 75%, or exceeded this level for only 15 minutes or less, did not develop so severe alterations. Some of the latter, however, showed what appeared to be degenerative changes of individual muscle fibers. These were most prominent in our chronic CO experiments.

It thus appears that in dogs severe changes in the myocardium are produced only if the CO concentration exceeds 75% and is maintained at this level for not less than between 15 minutes and 1 hour; while moderate alterations were observed following chronic exposure leading to a COHb concentration of 21%.

It had been noted by previous observers that the electrocardiographic changes from CO poisoning closely resemble those observed in anoxia whether induced by O₂ deprivation,^{9,14,18,22,23} pituitrin or adrenalin injection,⁹ exertion,^{4,9} anemia,⁴ high altitude²⁹ or fear.²⁷ A similar resemblance was found to exist between the morphologic changes in CO poisoning and those produced by anemia, exertion, or low O₂ tension.^{3,4,26} Klebs,²⁰ on the other hand, has pointed out that in man in CO poisoning, in contrast to asphyxia, no pleural hemorrhages were found; and Drinker¹⁰ has noted that in CO poisoning nervous symptoms invariably occur before respiratory symptoms, while in asphyxia the latter preceded the former. Though these observations cannot be disregarded, it seems that they do not speak against an anoxic nature of CO poisoning, for here we deal with a slowly rising concentration of CO in the blood, resulting in a slow asphyxiation; while the cases of anoxia which Klebs and Drinker had in mind possibly were those of sudden catastrophe or violence resulting in almost instant death of the patient.

Summary. All experiments were performed upon dogs. Acute CO poisoning was produced in some animals by inhalation of the gas and in others by intravenous introduction of erythrocytes saturated with CO; while chronic poisoning was effected by exposure to 0.01 vol. % CO for 5½ hours daily over a period of 11 weeks. As a control, chronic anoxia was produced in other animals by exposure to an atmosphere containing only 10 vol. % O₂.

The electrocardiographic changes observed were inversion of the T wave, elevation of the R-T segment, atrioventricular dissociation, and A-V heart block. The morphologic changes included certain degenerative changes of individual muscle fibers, as well as hemorrhages and necroses of the myocardium. While the changes in the T wave and R-T segment and the degenerative changes appeared as early as at 40% COHb in acute experiments, or at 21% COHb or an equivalent O₂ deficiency in chronic exposure, heart block and myocardial hemorrhages and necroses were observed only when the COHb level exceeded 75% for 1 hour or longer.

It was noted that the electrocardiographic and morphologic changes of the heart in CO poisoning closely resemble those observed in anoxia due to other causes.

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PROGRESS OF MEDICAL SCIENCE

OTO-RHINO-LARYNGOLOGY

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ACUTE LARYNGOTRACHEOBRONCHITIS: A 25 YEAR REVIEW

BY MAJOR A. HARRY NEFFSON, M.C., A.U.S.

SIGNIFICANT literature concerning acute laryngotracheobronchitis first appears in the wake of the 1918 pandemic of influenza. Having been accustomed to regard cases of acute laryngeal obstruction as invariably due to diphtheria, the early writers were surprised to find that a number of patients with acute obstructive infections of the laryngotracheal airway did not follow the usual clinical course of a diphtheria patient treated with antitoxin and, moreover, showed no Klebs-Loeffler bacilli on culture. Thus, it seems that it required the impact of an epidemic of influenza, with its striking complications involving the respiratory tract, to awaken the medical profession to the need for a critical reëxamination and overhauling of their traditional ideas concerning so-called "croup." This was 25 years ago. Since then many changes have occurred in our conception of this disease.

It is the purpose of this review to trace these changes in our conception of the various aspects of the disease—namely, as regards the nomenclature, bacteriology, pathology, symptomatology, diagnosis, supportive and specific treatment, operative and postoperative therapy and the recognition and treatment of complications.

Historical. The first references calling attention to acute laryngeal obstruction caused by organisms other than the Klebs-Loeffler bacillus are scattered case reports. McNab⁷⁶ (1915) reported 1 case with membrane which on culture yielded only *Strep. hemolyticus*; Morris⁷⁹ (1917) reported 3 cases of laryngeal stenosis as a complication of measles—all 3 died; Gardner³⁹ (1918) reported 3 cases of necrotic and exudative inflammation of the larynx, trachea and bronchi caused by the *Staph. pyogenes aureus*—all died and showed pneumonia on postmortem examination. Lewis^{63,64} (1918) reported 164 cases of membranous croup of which 61 were clinically diphtheria and 52 also bacteriologically diphtheria; in the rest (103 cases) only streptococcus was found. He said that cases of membranous croup are generally mistaken for diphtheria, whereas the streptococcus is the causative agent. He suggested the elimination of the term "croup" and "membranous croup" as misleading, and urged the use of the term "laryngitis." In the same year (1918) Gover⁴⁵ reported 96 cases of "membranous croup" of which 40 showed negative cultures for diph-

theria; also 74 cases of "non-membranous croup" in which 54 showed cultures negative for diphtheria. He stated, "It has been felt that in the past many of the croup cases were not diphtheritic, but only a catarrhal laryngitis." Lynah⁷⁰ (1919) said, "During the recent pandemic of influenza I had an opportunity to study the laryngeal and tracheobronchial pictures in influenzal patients. Some were supposed to have diphtheritic laryngitis until laryngoscopy showed otherwise. During routine direct examination of croup cases in the Willard Parker Hospital they were surprised to find no membrane present." In 1921, Jackson⁶⁷ and Purell⁹⁵ each reported a case of laryngeal stenosis not caused by the diphtheria bacillus. Thomson¹⁰⁸ (1922) reported that out of 810 patients admitted to the Willard Parker Hospital with a diagnosis of laryngeal diphtheria, 113 had "acute stenotic laryngitis" due to measles, scarlet fever, influenza, and other infections. In 1924, Smith¹⁰⁹ reported 4 cases in which only *Strep. hemolyticus* was found and Lynah⁷¹ reported 5 patients tracheotomized because of laryngeal obstruction, in all of whom only *Staph. albus* was cultured. In the same year Baum² reported 4 patients with laryngeal obstruction requiring tracheotomy in whom the causative agent was *Strep. hemolyticus*; he designated this condition as acute laryngotracheobronchitis, which presumably is the first reference to this term in the literature. In 1925 Dixon³² reported 1 case due to streptococcus and staphylococcus, and Strachan¹⁰⁶ reported 3 cases due to *Strep. hemolyticus*, staphylococcus and *B. influenzae* with fatal results. In the same year (1925) Lewis^{66,67} reported 4 deaths from membranous laryngotracheobronchitis complicating scarlet fever and caused by streptococcus. In 1926 Daily²⁷ reported 1 case and Allen and Husik⁶⁴ reported 2 cases of laryngeal obstruction requiring tracheotomy, in which the diphtheria bacillus was absent. Gittins⁴¹ (1926) reported 14 cases of non-diphtheritic laryngeal obstruction, mostly due to streptococcus. In 1932 he said, "The Klebs-Loeffler bacillus is blamed for many conditions it doesn't cause. In 1920 we realized for the first time that there are non-diphtheritic infections of the larynx, trachea and bronchi in which the onset and symptoms simulated diphtheria, but in which antitoxin gave no relief and the mechanical obstruction below the cannula was decidedly more troublesome than in diphtheria." Tucker¹¹¹ and Hart⁵⁰ (1927) each reported a case due to a non-diphtheritic infection, that of the former requiring tracheotomy. In 1928 Baum² reported 24 cases of acute laryngotracheobronchitis in children. In his discussion of Baum's paper, Forbes³⁷ asks, "Is acute laryngotracheobronchitis a comparatively new picture? Was it common before the great influenza pandemic 10 years ago? Why doesn't this serious complication of our seasonal epidemic respiratory infection receive more attention in our recent textbooks? (This question is still a valid one today.—ED.) Fifteen years ago we were taught in medical schools that laryngeal diphtheria is about the only disease requiring intubation. . . . In Denver in 8 years I have not treated 1 case of laryngeal diphtheria, but I've seen 15 cases of acute laryngotracheobronchitis requiring surgical intervention."

With this report by Baum,² in 1928, may be said to have come to an end the early phase of the conception of this disease. Since that time notable contributions to the various aspects of this subject have been made by Arden and Duhig,¹ Baum,²⁻¹⁰ Brennemann *et al.*,¹⁵ Davison,^{29,30} Galloway,³⁸ Gilbert *et al.*,⁴⁰ Gittins,⁴¹⁻⁴⁴ Holinger,^{52,53} MacCready,^{72,73} Michels,^{77,78} Neffson and Wishik,⁸¹⁻⁸⁹ Orton *et al.*,⁹¹ Richards,^{96,97} Sinclair,¹⁰¹ Tolle¹¹⁰ and others. These will be noted under the proper headings.

Nomenclature. Since Baum's suggestion in 1924, the term "acute laryngotracheobronchitis" has been coming into general acceptance as a designation for this condition. That this name is not completely satisfactory, however, is apparent from the statements of several writers.

Richards⁹⁶ (1933) stated, "We have been able to formulate a definite disease entity from a clinical and pathologic study of 11 cases recently encountered . . . fulminating laryngotracheobronchitis."

Neffson and Wishik⁸¹ (1934) defined the term "croup" as the symptom-complex due to any stenosis of the laryngotracheal air passages and proposed the term "acute infectious croup" to include all those cases of respiratory tract obstruction that were due to infection. Further, to those obstructions not caused by diphtheria, they gave the general designation "acute non-specific infectious croup" which included acute laryngitis, acute laryngotracheitis and acute laryngotracheobronchitis. Moreover, they urged that in describing each particular case, both the etiology and the extent of involvement be given whenever possible, *e. g.*, acute streptococcic laryngitis, acute staphylococcic laryngotracheitis and acute pneumococcic laryngotracheobronchitis. They warned of the tendency of certain workers to include relatively mild cases of laryngitis and laryngotracheitis in the more serious group of acute laryngotracheobronchitis, "which is characterized by extreme subglottic swelling associated with profuse secretions poured out from the entire extent of the tracheobronchial tree;" and they pointed to the . . . "value of an anatomic grouping from the standpoint of therapy, prognosis and as a basis for comparing results of different workers." They also differentiated these cases when they occurred as complications of the exanthemata.

Brennemann *et al.*¹⁵ (1938) stated, "A sharp differentiation according to the precise nature of the involvement in a given case is not always a simple matter, especially as one must find its exact place in a series of manifestations that range in severity all the way from simple catarrhal laryngitis to rapidly fatal fulminating laryngotracheobronchitis." Brighton¹⁶ (1940) wrote, "Only cases requiring tracheotomy should be considered as acute laryngotracheobronchitis." Orton *et al.*⁹¹ (1941), however, included cases in which surgical procedure was not needed. They said, "Every child with acute laryngitis is potentially a victim of acute laryngotracheobronchitis until proven otherwise. . . . In the early cases it is hard to differentiate them; after improvement it is also hard to tell them apart. Beginning as acute laryngitis, it may stay that way or go on to acute laryngotracheitis or acute laryngotracheobronchitis."

Gilbert *et al.*⁴⁰ (1941) stated, "Failure to standardize the nomenclature constitutes a challenge to those responsible for the care of patients with this disease. This challenge may be considered answered only after a proper classification of croup has been accepted. . . . A practical classification should automatically yield a clue to the appropriate management as well as to the immediate prognosis in each case of croup. . . . The term 'croup' designates a state of obstruction to the entrance of the air into the lungs as a result of an inflammatory process in the larynx or extending to the lower respiratory tract. There are two main types, diphtheritic and nondiphtheritic. . . . The term 'acute obstructive laryngotracheobronchitis' is used in preference to 'acute laryngotracheobronchitis' or 'acute fulminating laryngotracheobronchitis,' because the element of obstruction is the predominant feature. . . . 'Acute hemorrhagic necrosing tracheobronchitis,' associated with 'acute hemorrhagic pneumonitis' (so-called 'inflammatory pneumonitis'), but without subglottic edema should

not be included. Pneumonia with associated mild catarrhal inflammation of the laryngotracheobronchial tree is excluded. . . . Recently obstructive laryngotracheobronchitis has enjoyed prominence in the literature to the exclusion of most other varieties of croup. Careful analysis of the related pathologic conditions, symptoms and clinical data reported leaves considerable doubt as to the accuracy of diagnosis in some cases. . . . At present all types are placed in the group of acute laryngotracheobronchitis regardless of whether they have bronchial or pneumonic involvement or not." They present a "comprehensive classification" as follows: "Non-diphtheritic croup": (a) acute catarrhal laryngotracheitis, (b) supraglottic edematous obstructive laryngitis, (c) subglottic obstructive laryngotracheitis—(1) edematous type and (2) exudative or inspissated type—and (d) acute obstructive laryngotracheobronchitis.

Gittins⁴⁴ (1942) uses the term "infectious laryngotracheobronchitis" and calls the condition a symptom-complex. He classifies laryngotracheobronchitis into four types: infectious, traumatic, allergic and spasmodic. The infectious type he subdivides into "(a) nonspecific (streptococcus, staphylococcus, influenzal, pneumococcus, etc.) and (b) specific (diphtheria)."

MacCready⁷³ (1944) wrote, "In view of the pathology it seems unwise to refer to any of these cases, even the milder ones, as laryngitis alone. . . . The only patients in this series which fall into this group (laryngitis) died from profound inflammation of the glottis, before it had time to extend to the trachea and bronchi." (This seems to be a rather dangerous assumption, because cases of acute edematous obstructive laryngitis are often self-limited.—E.p.)

Baum¹⁰ (1944) said, "It (acute laryngotracheobronchitis) is not a specific clinical entity, but a symptom-complex. . . . There is a primary infection with the virus of influenza and a secondary invasion by the streptococcus. . . . It is a symptom-complex of different degrees of severity." Holinger,⁶³ discussing Baum's paper, asked, "When is it acute laryngitis and when acute laryngotracheobronchitis?" He said that pulmonary findings are an essential factor in the diagnosis and also stressed the disease as a symptom-complex.

Thus, it is evident that there is still need for agreement on an all-inclusive, general term denoting acute non-diphtheritic infectious obstruction of the laryngotracheobronchial airway, with (a) specific anatomic subdivisions indicating the extent of involvement and (b) possibly also pathologic descriptions of the cause of the obstruction. Acute laryngotracheobronchitis is only one phase of the whole picture; if used correctly the term describes the most severe and dangerous affection found in this condition. However, its frequent and casual application to cases with mild, moderate or even severe involvement of the larynx and trachea only, has led to much confusion when comparing types of therapy, prognosis and results of different workers.

That this disease is not a clinical entity, but rather a symptom-complex is gradually becoming apparent.

Bacteriology. Many organisms have been implicated as the agents in this disease. Not only have they varied in different localities, but also at different periods in the same locality. Since many of these cases occurred during epidemics of influenza, which at one time was thought to be caused by the *B. influenzae*, it was only natural for many to believe that this organism was the prime factor. However, since recent work has shown influenza to be caused by a virus, opinion has been veering to the view

that the various organisms recovered in this disease are merely secondary invaders in a soil made fertile by the virus of influenza. Some confusion has resulted from the fact that some writers still think of the *B. influenzae* as the etiologic agent in true influenza.

Chronologic reports of the bacteriology in this disease follow: McNab⁷⁶ (1915) 1 case—streptococcus; Gardner³⁹ (1918) 3 cases—*Staph. aureus*; Lewis⁶⁴ (1918) stated that streptococcus is the most common organism found; Smith¹⁰³ (1924) 4 cases—*Strep. hemolyticus*; Lynch⁷¹ (1924) 5 cases—*Staph. albus*; Lewis⁶⁶ (1925) 4 deaths in scarlet fever with laryngeal obstruction—*Strep. hemolyticus*; Dixon³² (1925) 1 case—streptococcus and staphylococcus; Strachan¹⁰⁶ (1925) 3 cases—all died—*Strep. hemolyticus*, staphylococcus and *B. influenzae*; Gittins⁴¹ (1926) 14 cases—streptococcus predominating, with staphylococcus and pneumococcus less frequently, *B. influenzae* occasionally; Hart⁶⁰ (1927) 1 case—*Strep. non-hemolyticus*; Leigh⁶² (1927) 4 cases—staphylococcus, pneumococcus and streptococcus; Berry¹³ (1928) 1 case—died—*Staph. aureus hemolyticus*. In 1930 Cultra and Streit²⁶ reported 13 cases in which the predominating organism was the staphylococcus; Bradford and Leahy¹⁴ reporting 28 cases found mostly *Strep. viridans*, only 5% *Strep. hemolyticus*. From Australia in the same year (1930), King⁶¹ reported 1 case in which no Klebs-Loeffler bacilli were found; Mathew⁷⁵ reported 4 cases with *Staph. aureus*; Beare¹¹ reported 10 cases—8 *Staph. aureus* and 2 pneumococcus. Richards⁹⁶ (1933) found *Strep. hemolyticus* in pure culture in all cases that came to postmortem examination; staphylococcus and pneumococcus were occasional secondary invaders. Neffson and Wishik⁸² (1934) reported the bacteriology in 254 cases as follows: Pure cultures—*Strep. hemolyticus* in 72 cases, *Strep. viridans* in 45 cases, *Staph. aureus* in 13 cases, *B. influenzae* in 3 cases; some type of streptococcus, alone or combined with other organisms, was found in 234 cases (92%); *Strep. hemolyticus*, alone or in combination, in 177 cases; *Strep. viridans*, alone or in combination, in 130 cases; *Staph. aureus*, alone or in combination in 71 cases; *B. influenzae*, alone or in combination, in 10 cases. Smith¹⁰⁴ (1936) reported 43 cases with *Strep. hemolyticus* in 26, *Strep. viridans* in 23, *Staph. aureus* in 17, pneumococcus in 5; in 4 fatal cases *Strep. hemolyticus* and *Staph. aureus* were recovered. Jackson⁶⁸ (1936) stated that the streptococcus was found in over 90% of the cases, the *B. influenzae* in 5%. From Puerto Rico, Font and Ortiz³⁶ (1939) reported 6 cases due to the *Staph. aureus hemolyticus*—3 died; they stated that there was no apparent difference between these cases and the ones caused by the *Strep. hemolyticus*. Neffson and Bullowa⁸⁵ (1938) reported a case of acute laryngotracheobronchitis with septicemia, meningitis and endocarditis due to *B. influenzae*. Sinclair¹⁰¹ (1941) reported 10 cases of laryngitis with septicemia due to *H. influenzae* type B. In these cases severe prostration accompanied the laryngeal obstruction. He quoted Pittman⁹³ who found that the pathogenic strains of *B. influenzae* are usually encapsulated and the capsules have a specific soluble antigen which renders them capable of differentiation into the serologic types A to F. The majority of strains isolated from influenzal meningitis are type B. Sinclair showed that the septicemias with laryngitis were due to type B. De Navasquez³¹ (1942) also cited a case of laryngitis with septicemia due to *H. influenzae* type B. Orton *et al.*⁹¹ (1941) reporting 45 cases found streptococcus in 11, streptococcus and staphylococcus in 13, streptococcus and pneumococcus in 10, staphylococcus in 4, pneumococcus in 2, streptococcus, staphylococcus and pneumococcus in 4, staphylococcus and pneumococcus in 1. Neffson⁸⁸ (1942) tracing the incidence of bacterial infections

in 126 tracheotomized cases during 1931-1940, found that there was a remarkable increase in the frequency of *Staph. aureus* infections since 1938; in fact there were twice as many infections with the *Staph. aureus* as with the *Strep. hemolyticus* during the period 1938-1940. On the other hand, during the period 1931-1934 there were 5 times as many infections caused by the *Strep. hemolyticus* as due to the *Staph. aureus*. Walsh¹¹³ (1944), reporting 101 cases, found the predominating organism to be a staphylococcus combined with streptococcus and pneumococcus; also some *B. influenzae* and 1 *B. friedlander*. MacCready⁷³ (1944) reported that 3 cases due to *B. influenzae* were treated in 1931 and 4 cases with septicemia due to *H. influenzae* type B were seen in 1941-1942; he states that there were none in 1943, but there were many with pneumococcus type 6. Arden and Duhig¹ (1944) report 5 cases in which *Staph. aureus* was recovered; there were 3 deaths; in 2 of these there was a necrotic laryngotracheobronchitis, in the other severe supraglottic edema.

Discussing a paper by Gittins in 1936, Baum⁷ expressed the view that the basic cause of acute laryngotracheobronchitis was the filtrable virus of influenza.

Brighton¹⁶ (1940) called attention to an almost identical disease of chickens—infectious laryngotracheitis—as shown by Beech¹² in 1931. He suggested that acute laryngotracheobronchitis in humans is the result of a virus infection with secondary invasions of the various bacteria which we have found. (Beech stated that there was in use a successful virus vaccine against this disease in chickens.)

Neffson⁸⁶ (1940) stated that there was a strong possibility that the recent epidemic may have been caused by a virus infection with secondary invaders, because (a) the laryngologic picture, with the more than usual amount of supraglottic edema and the tendency to ulceration, was similar to that found in measles, (b) the organism recovered was the same—*Staph. aureus*, and (c) the W.B.C. count was depressed just as in virus infections.

MacCready⁷² (1940) stated that acute laryngotracheobronchitis occurs sporadically during influenza and measles epidemics; furthermore, he said, "It used to be thought that the streptococcus was a factor, but now it is felt to be an influenzal type of infection with secondary invaders."

Orton *et al.*⁹¹ (1941) stated that they found no proof of virus infection, but the low blood count in some cases suggested virus disease.

MacCready⁷³ (1944) asserted, "While the virus may initiate the process, the symptoms produced by the bacterial or secondary infection may not necessarily occur concomitantly. They may not appear for 1 or 2 weeks. This directs most of the attention to the bacteria as the etiologic agent which it is necessary to combat in this disease. When pneumococci are present as the pathogens the picture is apt to be not as severe as with other pathogens . . . the *Staph. aureus* is . . . only a contaminant." He states that the *H. influenzae* type B causes the most serious symptoms and he suggests that it may bear a closer etiologic relationship to this disease than any of the other pathogens commonly found.

Arden and Duhig¹ (1944) reasoned that the fact that so many organisms have been incriminated and the similarity of this disease to that of laryngotracheitis in virus infections of chick embryos shows the close identity between the two diseases. From histologic studies (to be described later under Pathology) and comparisons with infectious laryngotracheitis and influenzal virus infections in chick embryos, as shown by Burnet and Folley,¹⁸ they conclude that, ". . . we believe that we are dealing with a disease

which has a specific and uniform pathology, which cannot be accounted for by any bacterial infection, but which . . . is due to a virus . . . (which) . . . is not an influenza virus . . . though there may be some relation between the two viruses."

Pathologic Anatomy. Winternitz *et al.*¹¹⁶ (1920), describing the pathology of influenza, stated that the mucosa of the trachea and bronchi is very red, covered with exudate and shows superficial ulceration, which does not result in scarring. The bronchioles are full of exudate and pus and ulcerations here often extend to the submucosa and the muscular layer; the ulceration may be local or the entire circumference of the tube may be involved. The inflammation occasionally extends down to the duct of the mucus gland, which is involved in an aplastic inflammatory reaction. In the early stages there is an outstanding absence of polymorphonuclear leukocytes.

Cultra and Streit²⁶ (1930), reporting 13 cases, described exudation of a thick sticky mucus and swelling of the larynx. The mucosa was congested and beefy red in appearance. They said that the dyspnea and cyanosis are caused by bronchospasm and the gluing together of the lumen. Beare¹¹ (1930) described 5 cases that came to postmortem examinations; there was intense inflammation of the larynx and trachea and a patchy atelectasis and emphysema of the lung.

The first comprehensive description of the pathology of acute laryngo-tracheobronchitis was given by Richards⁹⁶ in 1933. He stated that the changes were essentially those of an acute descending inflammation of the upper respiratory tract with the extent of the involvement depending upon the duration of life after onset of symptoms. He described (1) a diffuse acute cellular infiltration and destruction of the walls of the larynx, trachea and bronchi—the histologic picture being comparable to that of a cellulitis of the skin; (2) a second type of lesion was seen in the destruction of the mucosa and the masking of the mucosal surfaces by fibrin and purulent exudate; (3) in those cases where a superimposed infection with staphylococcus occurred, a more marked destruction of the mucosa and wall of the trachea was noted as a manifestation of the necrotizing characteristics of that organism; (4) in the lungs there was peribronchial reaction and polymorphonuclear infiltration of the alveolar walls. He mentions a case in which a child died suddenly 54 days after the original infection. Postmortem examination showed that the mucosa of the trachea had been repaired and replaced by stratified squamous epithelium; there was slight peribronchial infiltration and some mediastinal emphysema.

Neffson and Wishik⁸² (1934) described the "living pathology" as consisting of edema, exudation, membrane formation and spasm. The edema and congestion may be limited to the supraglottic or the subglottic structures, or may involve both and extend down to the bronchi. The exudation varies in amount and character. In mild cases it is scant or absent; in severe cases, with involvement of the trachea, bronchi and bronchioles, exudation is always profuse, usually thick and tenacious, and sometimes soropy that it cannot be expectorated. If it is not removed it becomes gummy, often hindering the separation of the vocal cords and plugging the subglottic regions. In this region it can become dry and hard and resemble a foreign body. Membrane is found in severe infections, but this is usually thin. In more virulent infections, thick membrane, indistinguishable grossly from diphtheritic membrane was removed from the larynx, trachea and bronchi. Postmortem examinations in 12 out of the 19 fatalities in their series of 400 cases showed pneumonia, atelectasis, emphysema,

empyema, mediastinitis, myocarditis and various other lesions secondary to septicemia. They also described the morbid anatomy in measles with laryngitis based on necropsies on 5 patients. In 4 cases there were extensive ulcerations of the larynx and trachea with exposure and erosion of the laryngeal cartilages and tracheal rings; pseudomembrane covered 2 of these ulcerated areas. Extensive bronchopneumonia was present in all 5 cases. It was also noted that in these patients there was a greater degree of supraglottic edema than in the usual run of non-specific cases.

Jackson and Jackson⁵⁸ (1936) described redness, swelling, secretion, the drowning of the patient in his own secretions, and crust formation. Richards⁹⁷ (1938), commenting on the low incidence of obstructing crusts, said this "... may have been due to more zealous attempts to provide adequate moisture in the inspired air or to the use of solvents instilled directly into the trachea ... associated with a lowered virulence of the infection and a fortunate absence of a secondary invasion by the staphylococcus." Clerf²³ (1939) stated that "The greatest pathologic finding is the marked subglottic swelling."

Brennemann *et al.*¹⁵ (1938), in an excellent description, stated, "The first signs of obstruction are usually due to the marked inflammatory swelling and edema of the loose subglottic tissue. If infection spreads, the same series of changes occurs in the trachea and bronchi except that with a less loose submucous tissue there is less swelling. The irritation of the infection is presumably the cause of the increased secretion of the tracheobronchial glands, the secretion being at first serous and later mucous. As the infection continues, not only are edema and acute inflammatory cells present in the submucous tissues, but other changes occur, such as extravasation of fibrin, fibrinoid degeneration of the connective tissue and lymphatic and capillary thrombosis. Simultaneously, the infection may cause necrosis of the epithelium, and exudate, fibrinous or fibrinopurulent, may be discharged onto the surface and become intimately mixed with the mucus which is being secreted. . . . It is apparently the mixture of mucus, fibrin, polymorphonuclear leukocytes and degenerated epithelial cells which make the typical gummy, ropelike exudate and the crusts. The mucous glands and excretory ducts seem to offer moderate resistance to the infection and hence do not appear to be altered anatomically early in the disease. As the disease progresses to its later and more severe stages, however, sufficient damage may be done to these glands themselves to cause various degrees of degeneration and necrosis. When sufficient glandular damage has occurred, no further mucus is secreted, and gray fibrinous or fibrinopurulent exudate is discharged on the necrotic surface, producing the dry, glazed appearance noted grossly at bronchoscopy and at autopsy. . . . Apparently this sustained glandular integrity and function, as judged from the bronchoscopic picture and the presence of relatively little anatomic glandular change, as compared with that of the surrounding tissue, until noticeably late in the disease, are somewhat different from the changes which occur in diphtheria, in which, according to Councilman, Mallory and Pearee,²⁵ the glandular necrosis is almost specific and may take place with little damage to the surrounding tissue. The principal difference, however, is in function, with undoubted stimulation in tracheobronchitis and suppression in diphtheria, the suppression being possibly due to the action of the soluble toxin in diphtheria. . . . The ropelike secretions and the dried crusts cause partial or complete obstruction to the bronchi and to the bronchioles, with resulting atelectasis and compensatory emphysema or obstructive emphy-

sema, the type depending on the degree of occlusion. Spontaneous pneumothorax may occur from rupture of an emphysematous bleb. Pulmonary edema, interstitial pneumonia, lobular pneumonia and septicemia are common complications in fatal cases."

MacCready⁷² (1940) stated, "Histologically the mucosa is destroyed over large areas and replaced by fibrin, mucus and red cells. The submucosa is edematous and congested. Similar changes occur in the smaller bronchioles. When *B. influenzae* was recovered the pathologic picture was less marked than with streptococcus; with the staphylococcus, necrosis is more pronounced."

Grier⁴⁹ (1941) described a characteristic mediastinal enlargement in acute laryngotracheobronchitis. The enlargement was found in the superior mediastinal shadow. It was symmetric and projected on both sides of the spine, the edges usually being concave, but occasionally straight. He differentiated this from the thymus shadow which is almost always a bulging shadow with convex borders.

Orton *et al.*⁹¹ (1941) reported their findings in 8 postmortem examinations as follows: Crusts and mucopus were found in the nose; the pharynx and tonsils were inflamed; the mucosa of the larynx, trachea and bronchi were red and swollen, with thick, somewhat adherent, mucopurulent exudate which separated easily from the underlying tract and left no gross area of erosion. The smaller bronchioles were red and contained glairy, bloody material. The glands at the hilus of the lungs and along the trachea and bronchi were enlarged and congested. The lungs showed patchy consolidation and the bronchioles contained tenacious mucopus. On microscopy the smaller bronchi were found filled with pus and the walls infiltrated with polymorphonuclear leukocytes. The lining epithelium was degenerated or missing in places. The alveoli surrounding these bronchi were distended with purulent exudate. The walls were swollen, the lining ulcerated, and the alveoli partly collapsed. There were areas of atelectasis, emphysema and bronchopneumonia. They stated that in streptococcal infections there is fiery redness and swelling of the subglottic and tracheal regions, while the true cords may show very little reaction. Later, necrotic and gangrenous pseudomembranes may be seen extending down to the tracheal bifurcation and into the main bronchi. First it is the subglottic edema. Later the membrane which causes the obstruction. In staphylococcal infections the inflammation is accompanied by the formation of dirty gray, thick, tenacious plugs which tend to dry and crust and rapidly cause marked progressive obstructive symptoms. Six of their 62 patients had a pseudomembrane in the larynx. Removal of these crusts leaves no mucosal necrosis, which occurs later in streptococcal infections.

Gilbert *et al.*⁴⁰ (1941) found that, in the subglottic exudative or inspissated type, the vocal cords are immobile, being separated by exudate or crusts with relief on removal of these obstructions. In the edematous type, the obstruction is due to edema and the interference with motion of the cords, preventing complete abduction. In acute obstructive laryngotracheobronchitis the tracheal lumen is so narrowed at times as to make the passage of the bronchoscope difficult or impossible. Patients with subglottic edematous obstructive laryngotracheitis can enjoy relief and progress favorably for several days after tracheotomy; then the airways will become obstructed with thick exudate. . . . Inasmuch as the transition is incident to the secondary infection, cases in which this occurred are not included in acute obstructive laryngotracheobronchitis. They state

that in supraglottic edema the lingual surface of the epiglottis is more involved than the laryngeal surface. They believe this type to be self-limited. (I concur in this observation, contrary to the opinion of some, *c. g.*, MacCready.—Ed.)

Neffson⁸⁸ (1942) presented sections of the larynx, trachea and bronchi demonstrating the following: metaplasia and ulceration of the epithelium and infiltration of the submucosa, mucous glands and muscles with plasma cells; necrosis of the epithelium and membrane formation; diffuse cellular infiltration of the tracheal bifurcation with monocytes and polymorphonuclear leukocytes and fibrinopurulent exudate replacing the epithelium and the necrotic duct of a mucous gland. In a case of measles with ulcerative laryngotracheobronchitis there was seen diffuse infiltration of the larynx, trachea and bronchi with plasma cells, denudation of the epithelium, infiltration and destruction of the mucous glands with desquamation of the glandular epithelium. In a case of scarlatinal laryngotracheobronchitis the larynx showed denudation of the epithelium, generalized edema, and diffuse polymorphonuclear infiltration extending down to the perichondrium, together with abscess formation. In a case of varicella with acute obstructive laryngotracheobronchitis, the larynx showed infiltration, necrosis and denudation of the epithelium, monocytic infiltration between muscle bundles, deposition of fibrin and purulent phlebitis; the trachea showed the same picture including desquamation of the glandular epithelium. He stated that there is often dense infiltration of the subglottic tissues, the formation of occasional strictures and webs (not due to intubation), and the occurrence of prevertebral edema with compression of the trachea, which are factors in delayed decannulation following tracheotomy. He also noted enlargement of the superior mediastinal shadow in roentgenograms of patients with acute laryngeal obstruction, as described by Grier. He describes several cases in which secretions accumulated in the trachea and bronchi in from 1 to 4 days following decannulation. In these cases aspiration of the airway was necessary. In 1 child 6 months old, the tube was removed and the wound closed 2 months after operation. The next day respiratory distress developed and was relieved by suction of the trachea and bronchi. This was done 3 times, the third time without relief. Postmortem examination showed thick mucus in the trachea and bronchi, which caused asphyxiation. There was no tracheal stenosis. (Possibly the observation of Hilding that ciliary destruction occurs in these cases could explain the accumulation of the mucus.—Ed.)

Hilding⁸¹ (1943) described a case of acute laryngotracheobronchitis in an adult. At necropsy the entire bronchial tree was found to contain thick, tenacious plugs of mucus. Microscopic examination revealed that the entire bronchial and bronchiolar epithelium had been sloughed off down to the last layer of stellate cells next to the basement membrane; there was not a vestige of a cilium anywhere. The lumens were filled with purulent exudate. He stated, "This patient would probably not have died of asphyxia had the ciliary mechanism been there to remove the thick secretion. Conceivably, aspirations through a tracheotomy might have saved him."

Baum⁸ (1943) stated that the outstanding lesions are mucosal and submucosal inflammatory edema, most marked in the looser connective tissue of the subglottic region, but extending down to the trachea and bronchi. Later there are exudation and destructive lesions. Laryngotracheobronchitis causes serious alterations in the function of the tracheobronchial

glands and in the character of their secretions. He asserted that these changes make the glands and the secretions more susceptible to adverse influences such as the drying effect of the direct blast of even warmed and moistened air through the tracheal cannula. He said that no one has reported primary plugging of the bronchi with crusts, without tracheotomy.

Walsh¹¹³ (1944) found (1) destruction of the epithelium and cilia, (2) tenacious thick pus and mucus which in severe cases seemed to be fixed to the goblet cells of the remaining epithelium and (3) marked edema of the tracheal and bronchial tissues. He said that bronchoscopy did not always give relief, showing that laryngeal edema is not the primary factor. On the other hand, bronchoscopic suction with removal of the thick secretions did give relief.

Arden and Duhig¹ (1944) described widespread necrosis of the mucosa unaccompanied by any cellular exudate. When the crust and exudate were removed, the underlying trachea was seen to be a dirty, brownish purple color, completely lacking luster, and quite different from the bright, purplish red commonly found in influenzal infections. The exudate extended to the main bronchi. Histologically there was complete destruction of the mucosa, with no cellular exudate, only debris, and submucosal vascular dilatation with some lymphocytic infiltration. They remark that this is unlike a bacillary infection, but resembles a virus infection. They found complete integrity of the mucus-secreting glands and their ducts (unlike that seen in diphtheria). Also, they did not find the typical lung involvement as in an influenzal virus infection; therefore, they reasoned that this was not of influenzal virus origin, though there is a relationship between the two viruses.

Incidence. *Frequency.* Orton et al.⁹¹ (1941) state that, "In all over 300 cases have been reported since 1918." They apparently overlooked the report in 1934 by Neffson and Wishik⁸² of 400 consecutive cases admitted between 1931 and 1934 to the Willard Parker Hospital because of non-diphtheritic laryngeal obstruction. This makes over 700 cases, not counting the number that have occurred without ever having been reported.

Seasonal. In the above-mentioned report by Neffson and Wishik, the disease was found to be "endemic the year round with a low ebb in June, July and August." However, Baum⁹ (1943) and others state that the disease is seasonal and more severe during influenza epidemics. It is quite possible that the difference in conclusions arises from the fact that diseases of different etiology, but similar symptomatology, are involved.

Age. Berry¹³ (1928) reported a case in an adult with crusting and suppuration of the entire respiratory tract, in which a pure culture of *Staph. aureus hemolyticus* was recovered; Davis²⁸ (1936) likewise reported a case in an adult. Michels⁷⁸ (1942) reported a case in an infant 5 weeks old. Neffson and Wishik,⁸² in their series of 400 cases, found the age to range from 3 months to 50 years; 11.7% were under 1 year; 46% were 1 and 2 years old; 78% were under 5 years of age; 16.5% from 5 to 9 years; 5.5% were over 9; 11 patients were over 16 years of age.

Sex. It is generally agreed that this condition occurs more often in males than females. Specifically, the report of Neffson and Wishik⁸² showed that there were 72% males as compared to 28% females. Neffson⁸⁸ (1942), reporting a series of 126 cases tracheotomized for non-diphtheritic laryngeal obstruction, found that 70% were males and 30% females. This shows that males are affected almost $2\frac{1}{2}$ times as often as females. Why this should be so, since the large majority of cases occur under 5 years of age, is a matter of conjecture at the present time.

Symptomatology. A general description of the symptomatology is given by almost every writer on this subject. Briefly, there are hoarseness, cough, signs of respiratory obstruction and the usual reactions to infection, namely fever, leukocytosis and evidence of toxemia—with much variation both in the rapidity of onset and the degree of severity. Because of the lack of unanimity as to what constitutes acute laryngotracheobronchitis, descriptions of the symptomatology are quite varied. Thus, some describe respiratory obstruction of moderate degree and little or no signs of toxemia, whereas others picture patients suffering from extreme respiratory obstruction and toxemia of overwhelming proportions. In some cases the respiratory obstruction required operative intervention such as intubation or tracheotomy, while in others palliative measures alone were sufficient.

For the purposes of this review it is felt that only those observations describing unusual or characteristic signs and symptoms of value in diagnosis need be noted.

Mainzer⁷⁴ (1929) stated, "Infections of this type may easily be mistaken for laryngeal diphtheria, but in these (latter) cases the voice is usually lost." Neffson and Wishik⁸² (1934) pointed out that cough occurred first, followed by dyspnea and later by hoarseness. They noted that this was different from diphtheria in which there is cough, followed by hoarseness and later dyspnea. They explained this difference on the basis of the underlying pathology, namely that in diphtheria membrane forming on the vocal cords, first prevents them from vibrating and approximating normally, causing hoarseness. Later, when enough membrane has formed dyspnea appears. On the other hand, in the non-diphtheritic case, edema is usually produced above and below the vocal cords and often the cords themselves are not involved, because the submucosa is bound down tightly. They also note that in the non-specific infection the dyspnea is usually out of all proportion to the slight or moderate hoarseness. Orton *et al.*⁹¹ (1941), however, stated that in over 50% hoarseness occurred early and was preceded or followed by a croupy cough. Later there was dyspnea, retraction, pallor and cyanosis. Jackson and Jackson⁹⁸ (1936) noted a weak or absent cough reflex. (I have observed this especially in cases of influenzal laryngotracheobronchitis and in those cases in which there was marked obstruction in the bronchi.—Ed.) Baum⁸ (1943) stated that with increasing obstruction the cough diminishes or disappears and there is a fall in temperature with a pale cyanosis due to diminished oxygen and circulatory exhaustion. When the obstruction is relieved the temperature rises. (I have never found a fall in temperature with increasing obstruction; on the contrary I have seen it rise and then fall after relief of the obstruction.—Ed.)

Sinclair¹⁰¹ (1941) describing cases of laryngitis with septicemia due to the *H. influenzae* type B noted that the appearance of shock seemed to be out of all proportion to the short duration of the obstructive symptoms, and that after a tracheotomy most of these failed to show immediate improvement. He considers that these are the most seriously sick group. Neffson and Bullock⁸⁶ (1938) made a similar observation in reporting a case of laryngotracheobronchitis with septicemia and meningitis due to the *H. influenzae* and complicated by a simultaneous, bilateral, spontaneous pneumothorax.

Leigh⁶² (1927) described a sudden death in a child 1½ years old occurring during an injection of antitoxin; on postmortem examination extreme supraglottic edema was found. Beare¹¹ (1930) describing the symptom-

atology said, "Finally . . . The picture may be that of a fairly quiet respiration, an alert mind, and a sudden death on attempting to sit up or after a moderate coughing seizure." Death was thought to be of cardiac origin. (The likelihood is that supraglottic edema was the cause of the sudden asphyxia; I have seen these sudden deaths due to supraglottic edema not only in a number of children, but also in several adults.—Ed.)

Neffson⁸⁴ (1937) described characteristic respiratory sounds as an aid in the diagnosis of supraglottic laryngeal edema. These sounds consist of a low-pitched inspiratory stertor with a louder and lower-pitched, coarse, expiratory rattle resembling a snore. In extreme supraglottic edema, only the expiratory component may be present—namely, the loud, low-pitched, coarse rattle; on inspiration there is either a somewhat muffled, high-pitched stridor or none at all. He warns that such patients should be taken to the hospital at once for laryngoscopic confirmation of the diagnosis and usually immediate tracheotomy should be performed because of the danger of sudden asphyxia.

Diagnosis and Differential Diagnosis. As has been remarked previously, one of the main obstacles in the way of correct diagnosis has been due to the tendency to exaggerate the extent of involvement in a given instance—that is, cases of obstructive laryngitis or laryngotracheitis have been diagnosed acute laryngotracheobronchitis. Sometimes this has occurred because of the difficulty in estimating the true status, sometimes because of lack of familiarity with the problems peculiar to diagnosis in this condition, and often because of the natural propensity on the part of some of our colleagues to prove their abilities in the face of greater odds.

The diagnosis of acute laryngotracheobronchitis requires clear proof of a non-diphtheritic infection involving the larynx, trachea and bronchi and causing serious obstruction to breathing. The diagnosis of bronchial involvement must be based upon a profuse and repeated outpouring of secretions, which results in repeated blocking of the airway.

In general, acute laryngotracheobronchitis must be differentiated from diphtheritic infections, laryngeal complications of the exanthemata, allergic manifestations such as bronchial asthma, and from foreign bodies.

Neffson and Wishik⁸¹ (1934) listed over 80 conditions which could be confused with acute laryngotracheobronchitis. They divided these under 8 headings—namely, (1) congenital malformations, (2) neuromuscular-spasmodic and paralytic, (3) tumors of the wall of the larynx or trachea, (4) occlusion by masses outside the airway, (5) plugging of the lumen by foreign matter, (6) traumatic, (7) edema of the larynx secondary to systemic disease, and (8) infectious, including blood dyscrasias.

Gilbert *et al.*⁴⁰ (1941) divided laryngeal obstructions into two groups, (1) infectious, including diphtheritic and non-diphtheritic croup; and (2) unclassified, including conditions due to allergy, foreign bodies, chemicals and other irritating agents.

Gittins⁴⁴ (1942) presented the following classification: "(1) Infectious types—(a) non-specific—streptococcic, staphylococcic, influenzal, pneumococcic; and (b) specific—diphtheria. (2) Traumatic. (3) Allergic. (4) Spasmodic."

Complications. Discussion of the complications in acute laryngotracheobronchitis, particularly those secondary to infection and septicemia, are beyond the scope of this review. However, tension pneumothorax and mediastinal emphysema, which are complications incident to acute respiratory obstruction and tracheotomy, have been receiving well-deserved prominence in recent literature and merit consideration here.

Wilks and Moxon¹¹⁵ (1875) cited 2 cases of pneumothorax following tracheotomy in which there was extensive mediastinal emphysema; they asserted that the air from the mediastinum ruptured through the pleura.

Champneys²¹ (1882 and 1884) reported 19 cases of mediastinal emphysema including 4 cases of pneumothorax occurring in 56 tracheotomy cases in which death resulted. He stated, "Pneumothorax . . . never occurred without emphysema and . . . was probably a later sequel of the emphysema. . . . Air was observed escaping from the mediastinum into the pleural sac. . . . It appeared, then, that the air traveled from the tracheotomy wound into the mediastinum, which in some cases it ruptured, producing pneumothorax." He advised that postmortem examinations be performed under water in order to avoid missing a pneumothorax.

Iglauer⁵⁶ (1915) described the case of a child with severe inspiratory distress. Before opening the trachea he noted bubbles of air at the lower angle of the wound. Immediately after tracheotomy the child collapsed, became almost pulseless and had extreme pallor. Roentgenologic examination showed right-sided pneumothorax.

Wiethe¹¹⁴ (1933) reported 2 cases of pneumothorax in a series of 50 tracheotomies. He stated that when respiratory obstruction is present the apex of the pleura can easily be injured while performing a low tracheotomy.

Neffson and Wishik⁸² (1934) cited 4 cases of pneumothorax complicating tracheotomy and 2 cases of pneumothorax in which no tracheotomy was performed. They explained, ". . . the air was sucked into the wound and passed alongside the trachea into the mediastinum, later rupturing through the pleura to cause the pneumothorax. All these patients had subcutaneous and mediastinal emphysema. . . . The occurrence of such emphysema following tracheotomy is due to the fact that the obstruction . . . was only partially relieved by the operation. As a result, the retractions continued and led to the sucking-in of air through the wound." They explained the 2 cases of spontaneous pneumothorax as follows: "Air, extravasated into the cellular tissue of the lung, spreads along the bronchi and vessels to the hilus and thence to the mediastinum . . . it may also appear immediately subjacent to the visceral pleura. Rupture of such a vesicle leads to pneumothorax. . . ."

Simpson¹⁰⁰ (1937) reported a case of pneumothorax complicating tracheotomy in fulminating laryngotracheobronchitis.

Richards⁹⁷. (1938) described 2 cases with pneumothorax. In 1 case, postmortem examination showed emphysematous blebs in the mediastinum; there was no break in the pleura; the bronchi were full of obstructive masses. The other case occurred in a 2 months old infant; there was no postmortem examination. He said, "Pneumothorax secondary to pulmonary emphysema is a complication present more frequently than hitherto appreciated."

Brennemann *et al.*¹⁵ (1938) stated that, "Spontaneous pneumothorax may occur from rupture of an emphysematous bleb."

Neffson and Bullowa⁸⁵ (1938) described a case of bilateral tension pneumothorax and commented on the mechanism of production of pneumothorax and mediastinal emphysema as follows: "The obstruction of the bronchioles by exudate and the marked supraglottic edema combined to produce violent inspiratory efforts. The dilatation of the bronchioles caused by the strenuous inspiratory efforts and the concomitant diminution of their contractile . . . power caused by the influenzal infection

resulted in overdistention and coalescence of the functioning pulmonary alveoli. . . . As a result, . . . certain of the emphysematous lobules burst. If they were subpleural, air passed into the pleura. . . . If the tear is not into the pleura, the air is forced into the pulmonary interstitial tissue and travels along the loose tissue surrounding the blood- and lymph-vessels and bronchi to the root of the lung, where it either ascends between the mediastinal fascial planes and appears in the neck, spreading down from this point or, more rarely, descends into the retroperitoneal space and perirenal tissues. If there are adhesions between the visceral and the parietal pleura, air may appear in the thoracic wall without traveling down from the neck."

Michels⁷⁷ (1939) reported 5 cases of pneumothorax and 1 case of mediastinal emphysema complicating tracheotomy. Three of the cases had bilateral pneumothorax and died. Michels concluded that occurrence of pneumothorax and mediastinal emphysema can best be explained as follows: "The extrapleural route, with dissection of minute globules of air from the interstitial tissues along the vessels to the hilus, is a more common cause of their occurrence with increased intrapulmonic pressure. . . . The dissection of air by way of the pretracheal fascia to the mediastinum, aided by the negative inspiratory pressure, affords another avenue of entry. The possibility of direct injury to the pleural dome during tracheotomy cannot be ignored."

Graebner⁴⁷ (1939) reported 3 cases of pneumomediastinum and 2 cases of pneumopericardium associated with acute obstructive laryngitis. He said, "The air was passed out of the substance of the lung and along the perivascular sheaths into the mediastinum by excess positive pressure incident to respiratory obstruction (rather than being) sucked in through the tracheotomy wound by inspiratory efforts and normal negative pressure in the mediastinum."

Dolgopol and Stern³³ (1940) described a case of pneumothorax which appeared 3 days after tracheotomy. On postmortem examination, the lungs showed alveolar emphysema, interstitial emphysema with large air bubbles in the widened, edematous interlobular septums, and air in the perilymphatic spaces. There was no mediastinal emphysema. The authors concluded that the air had traveled from the septal lymphatics to the periphery of the lung, and then escaped through rupture of pleural blebs into the pleura.

Neffson⁸⁹ (1942) reported 17 cases of pneumothorax in a series of 126 tracheotomies and gave a comprehensive discussion, including a review of the literature, of this condition. He describes the mechanism of its production as occurring *via* the following routes:

"I. *Intrinsic Route*. Increased intrapulmonic pressure caused by trapping of air results in distention and, finally, rupture of the pulmonary alveoli. . . . Such ruptures may be microscopic, numerous and widespread or gross and limited to one area. From these ruptures the air can then spread into the following tissues: (A) Pulmonary interstitial tissue . . . and thence . . . (1) To the hilus of the lung . . . producing mediastinal and pericardial emphysema. From the mediastinum the air can proceed . . . (a) Laterally. Rupture of mediastinal blebs into the pleural cavity results in pneumothorax . . . (b) Upward . . . breaking through into the subcutaneous tissues of the neck. (c) Downward . . . to the abdomen. (2) To the periphery of the lung . . . through pleural adhesions into the pleural cavity . . . (B) Subpleural tissue forming subpleural blebs which burst . . . This is uncommon, however . . .

"II. *Extrinsic Route*. Owing to inspiratory obstruction, the negative pressure in the thorax is increased, and air is sucked through the tracheotomy wound along the deep cervical fascia into the mediastinum From the mediastinum the air can reach the pleura, neck and abdomen in the same manner as described for the intrinsic route. This route is probably the more common after tracheotomy.

"III. *Traumatic Route*. . . . by injury to the dome of the pleura during tracheotomy However, actually it is probably rare"

He analyzes the 17 cases of pneumothorax, ". . . as to age, sex, site, time of occurrence after tracheotomy, relationship to previous intubation, incidence in relation to frequency of tracheotomy during various periods, time required for the disappearance of free air, mortality rates under various conditions and postmortem observations."

He finds that "The mortality rate of unilateral pneumothorax is less than 20%; that of bilateral pneumothorax, over 90%." He stresses that "early recognition and immediate treatment of this condition are life-saving. The possibility of the occurrence of tension pneumothorax must always be borne in mind and watched for after tracheotomy." Warning signs of pneumothorax and mediastinal emphysema are described, and the prophylaxis and treatment are outlined.

MacCready⁷³ (1944) stated, "Between 1941 and 1943 there were 6 cases of tension pneumothorax and mediastinal emphysema. Five had a preliminary bronchoscopy or the bronchoscope was passed in order to facilitate the tracheotomy. Instead of eliminating respiratory effort during the tracheotomy and hence preventing this accident from happening, these figures would suggest that it is the cause of the trouble These cases should be regarded as operative accidents." (In the light of the experience of most operators, these conclusions are untenable. Pretracheotomy bronchoscopy is advisable in order to guarantee an unhurried tracheotomy. If a bronchoscope does not relieve the dyspnea, the obstruction must be in the bronchi and bronchial aspiration should precede tracheotomy. There are some unfortunate cases in which that too is of no avail. But failure in these cases should not prejudice us against this procedure in the usual case.—Ed.)

Treatment. Treatment can be divided into two main types—medical and operative. Medical treatment is made up of non-specific or supportive therapy and specific therapy; surgical treatment consists of aspiration (suction), intubation, tracheotomy and postoperative care. It is the plan of this review to discuss the advances, changes and moot questions in treatment under these separate groupings.

Medical Treatment. I. *Supportive*. A word of caution is in order at this point; we must not allow the glare of sulfonamide therapy to blind us to the value of supportive treatment, a value which cannot be overestimated.

Most authors have advised complete rest in bed, a cleansing enema, steam inhalations, mild sedation, antipyretics, plenty of fluids, and small doses of codeine to allay excessive coughing. All agree that atropine and morphine are definitely contraindicated.

Neffson and Wishik⁸² (1934) stress the importance of antipyretics in order to reduce high fever, thus lowering the metabolic rate and consequently the oxygen requirement. They also advise administration of oxygen by nasal catheter or placing the patient in an oxygen tent to tide him over the acute stage for from 12 to 24 hours, when the edema usually begins to subside,

Kernan and Barach⁶⁰ (1937) advise the use of helium and oxygen under pressure.

Felts³⁵ (1940) recommended atmospheric supersaturation with moisture.

Davison^{29,30} (1940) emphasized atmospheric temperature and humidification. By the employment of a mechanical humidifier, he raised the humidity to 95 % with the temperature of 70° F. He found that loss of body water can be decreased by increasing the humidity provided that the temperature is not above 70° F. He stated that the temperature and humidity of an oxygen tent exert a greater effect on the comfort of the average patient than does the concentration of the oxygen.

Baum^{8,9} (1943) suggested the use of hypertonic human plasma in order to decrease subglottic and tracheobronchial edema before surgery in urgent cases. He stated that the plasma does not cure, it merely decreases the edema. He says, "I have seen little patients showing the typical pale cyanosis of partial asphyxia with exhaustion respond in a very gratifying manner. Stridor disappears, respirations quiet down, cyanosis rapidly fades and the patient falls asleep. This all occurs within a matter of minutes after the administration of the plasma is completed. Then the entire clinical picture usually continues to improve, especially if sufficient quantities of immune serum have also been administered and the patient soon has remaining only a simple non-obstructive tracheobronchitis and laryngitis from which recovery is rapid." He also advises the use of cooled humidified oxygen. He finds that the concentrated plasma does not cause dryness, stickiness or increase plug formation; on the contrary it helps to normalize the secretions.

Holinger⁵³ (1944) also advised a humidity of 90 % and a temperature of 70° F.; the use of 50 % hypertonic glucose has been abandoned by him.

Walsh¹¹³ (1944) recommended the use of a Burgess box in which 95 % oxygen and 5 % carbon dioxide is piped through an ice-box electrically driven.

Hypodermoclysis, infusions and blood transfusions have been advised by various workers.

II. *Specific.* Specific treatment has consisted of (1) vaccines and serums, (2) bacteriophage, (3) sulfonamides, (4) penicillin. Baum³ (1928) urged the use of vaccines, pooled antistreptococcic serums and specific immune serums. Richards⁹⁶ (1933) advised the use of bacteriophage and antistreptococcic serums. Neffson and Wishik⁸² (1934) used *Staph. aureus* bacteriophage in a number of cases with striking results in several.

Evans³⁴ (1939) used bacteriophage in order to liquefy secretions and reported 3 recovered cases—the organism was not named. In 1940, Davison,³⁰ Brighton¹⁶ and Neffson⁸⁶ each recommended the use of sulfonamide therapy. Sinclair¹⁰¹ (1941) reported 10 cases with *H. influenzae* septicemia complicating acute laryngotracheobronchitis; 6 patients received adequate sulfa therapy and recovered, the other 4 did not and died.

Orton *et al.*⁹¹ (1941) reported 38 cases in which no sulfa therapy was used; there were 9 deaths. Sulfanilamide was used in 20 cases; 13 recovered. Sulfapyridine was given to 3 patients; 2 recovered. In 15 cases sulfa therapy and surgery was needed; 7 patients recovered. In 8 cases sulfa therapy was given and no operation was needed; all recovered. They conclude, "It is possible that in many cases in which the sulfonamides were given, the disease was in a mild form We believe that, although the sulfonamides are not specific for this disease, they seem to have some value."

Neffson⁸⁸ (1942) reported that 81 cases requiring tracheotomy had been

observed since the advent of sulfa therapy. In 28 cases no chemotherapy was used; 11 deaths occurred—a mortality rate of 40%. Inadequate therapy was given in 11 cases—there was 1 death. Adequate therapy was given in 42 cases; there were 9 deaths—a mortality rate of 21%. Many patients died before they could be given the drug. Inadequate therapy was due to toxic manifestations, lack of improvement or acute aggravation of the illness. He found it difficult to draw conclusions as to the effect of the drug on the mortality rate. However, he concluded, “. . . chemotherapy has resulted in a decrease in complications, particularly pneumonia and septicemia, and has probably lowered the mortality rate. However, the local condition has not been affected sufficiently to lessen the need for mechanical intervention.”

Baum⁹ (1943) advocated the use of human immune serums, especially specific influenzal convalescent serum. In 1944 he stated that sulfa therapy is unsatisfactory because the disease is not due to the streptococcus; penicillin may be of more value. He asserted, “Human immune serum is best . . . it raises the titre of antibodies and also contains some influenza antibodies, especially after an epidemic.”

Walsh¹³ (1944) advises full doses of sulfadiazine intravenously or subcutaneously; 0.1 gm. per kg. body weight, totaling 0.3 gm. per kg. body weight for the first 24 hours, then 0.2 gm. per kg. per day.

Holinger⁵³ (1944) stated that sulfa therapy decreases the morbidity and has obviated the need for tracheotomy in many cases.

Arden and Duhig¹ (1944) reported 3 deaths in 5 tracheotomy cases in which *Staph. aureus* was recovered; sulfathiazole and sulfapyridine had been given.

MacCready⁷³ (1944) recommended giving sodium sulfadiazine in saline—dosage 1 gr. per pound per day, with one-half as the initial dose. The blood level should be kept at 10 to 12 mg. per 100 cc. He stated that every one of the 73 patients that received adequate sulfonamide therapy recovered except the last patient who died on the 6th day with mediastinal emphysema. He concluded, “Since the treatment of these patients is essentially the same as that of the 1933 period in all respects except for the use of the sulfonamides, any noticeable differences should be considered as resulting from the use of these drugs.” (This is not strictly true because the profession has become more aware of the problems in this disease, the supportive treatment is better and postoperative care has improved considerably.—Ed.)

Surgical Treatment. Operative intervention should be resorted to only after medical treatment has failed or has been deemed inadequate. Three procedures are available, depending upon the indications, namely aspiration, intubation and tracheotomy, with direct laryngoscopy a necessary adjunct in each instance.

Laryngoscopy. Scitz⁹⁸ (1929) stated, “When done by a skilled operator, laryngoscopy will not superimpose any noteworthy degree of traumatic inflammation and an anesthetic is not required.”

Neffson and Wishik⁸¹ (1934) stated, “A direct, diagnostic laryngoscopy should be performed in every case of croup in which there is the least doubt as to the nature of the infection . . . In skilled hands the procedure takes no more than 15 to 30 seconds, and the patient suffers very little discomfort . . . Diagnostic laryngoscopy is indispensable . . . in the treatment of croup.”

MacCready⁷² (1940) asserted, “Laryngoscopy should not be done . . . it may precipitate an acute edema, unless one is prepared to do an imme-

diate tracheotomy." (My experience with over 2000 laryngoscopies does not bear out this observation. Moreover, the anatomy of the epiglottis is such as to hinder edema formation on the laryngeal surface, which is the surface in contact with the laryngoscope.—Ed.)

Aspiration. Lynah⁶⁹ (1916) described bronchoscopic suction in the treatment of laryngotracheobronchial obstruction, particularly diphtheritis.

Litchfield and Hardman⁶⁸ (1923) used French-woven catheters for suction of the larynx.

Gover and Hardman⁴⁶ (1923) introduced the use of metal suction tubes for tracheobronchial aspiration through the laryngoscope.

Tolle¹¹⁰ (1930) reported a large series of cases in which she used Willard Parker metal suction tubes.

Neffson and Wishik⁸¹ (1934) described a curved, spiral-tipped metal suction tube for use in bronchial aspiration through the laryngoscope. They advocated the use of suction "when the obstruction is caused by tenacious, ropy, gummy, inspissated or membranous secretions." They conclude that "the suction treatment has eliminated the need for intubation or tracheotomy in many cases and is an essential adjunct when intubation is required. It has removed the danger of sudden asphyxia which formerly attended intubation because of the jamming down of membrane . . . or exudate . . . by its use both morbidity and mortality have been materially reduced."

Intubation. Most authors mention intubation only to condemn it. The most emphatic denunciation that I have heard was one delivered by Dixon in a discussion of Baum's paper on the treatment of acute laryngotracheobronchitis at the 1944 A. M. A. Convention, where he said that O'Dwyer was erroneously honored for the invention of the intubation tube, because it causes suffocation from obstruction of the tube by membrane. He said that it should not be used even in diphtheria, because it has resulted in many unnecessary deaths. Apparently he has forgotten how many thousands of lives this device has saved when properly used. Intubation should always be used in conjunction with aspiration except in an emergency in which case anything possible is done at the spur of the moment. Inexperience with, misuse or abuse of intubation is no reason for condemning this procedure. There are two methods to perform an intubation: (a) the indirect or tactual method which is done by palpation, and (b) the direct or visual method through a laryngoscope. The latter is preferred in order that the underlying pathology in the larynx may be visualized at the same time.

Morris⁷⁹ (1917) reported 3 cases following measles; all 3 were tracheotomized and all 3 died. He advised intubation in these cases. (Neffson and Wishik found that intubation in measles resulted in a high mortality rate and advised tracheotomy. Apparently relief of the obstruction is not the sole answer to this problem.—Ed.)

Gittins⁴¹ (1926), reporting 14 cases, concluded that intubation is not advisable. In 1936, he⁴³ reported 32 cases, of which 20 were tracheotomized with a mortality rate of 60%. Again he favored tracheotomy as compared to intubation. Hart⁵⁰ (1927) reported a case and advised that intubation be performed before tracheotomy. Baum³ (1928) stated that he kept intubation tubes *in situ* for a period of 3 weeks when necessary. He concluded, "Intubation is the operation of choice." Codd²⁴ (1931) reported 2 cases and advised tracheotomy in preference to intubation. Peeler⁹² (1926) believed that intubation is contraindicated in non-diphtheritic laryngitis. Bugg¹⁷ (1931) stated that he preferred intubation to

tracheotomy. Hyde and Ruchman⁵⁵ (1931) concluded, "Intubation is not advisable because, first, the edema may be very low and the tube would not pass the swelling; second, the edema may be so marked that it is impossible to pass the tube, thereby causing injury to the tissues and resulting in a false passage and emphysema." (I saw this happen only once, in the hands of an inexperienced interne, in a patient with a cleft palate.—Ed.) "A tracheotomy is advisable because in subglottic edema the chances of recovery are more rapid because of the absence of any irritating object in the larynx. If in doubt as to the cause of the edema one should institute tracheotomy instead of intubation."

Richards⁹⁶ (1933) decided in favor of tracheotomy *versus* intubation.

Neffson and Wishik⁸² (1934) stated, "... when the obstruction is due mainly to subglottic edema, intubation is helpful and far less dangerous than routine tracheotomy." They warned against its use in cases of supraglottic edema saying it "... may give some relief but may also irritate the inflamed supraglottic tissues, causing an increase in the edema. This may cause an overlapping of the tube and may result in sudden asphyxia . . . necessitating an immediate, urgent tracheotomy." They concluded, "However, this method of treatment is practicable only in hospitals where proper facilities and expert operators are available *at all times*."

Greenwood⁴⁸ (1939) believed that in infants a low tracheotomy conserves the laryngeal structure better than intubation.

Orton *et al.*⁹¹ (1941) stated, "Intubation tides a patient over until a tracheotomy can be done. Intubation is a deciding factor in the reaction of dyspneic patients from respiratory shock, except in cases where there is supraglottic swelling when tracheotomy must be done at once."

Neffson⁸⁸ (1942) lists the indications, the advantages and disadvantages of intubation and concludes that "... intubation performed before tracheotomy—in selected cases—is beneficial in that it gives the organism a chance to fight the acute infection before it is compelled to cope with the added burden of an operative procedure and to accustom itself to an alien respiratory mechanism and physiology, with all that this implies."

Baum¹⁰ (1944) stated that he favors intubation over tracheotomy, since the latter results in the formation of dried plugs. He advises that after tracheotomy an intubation should be performed and the tracheotomy tube corked so that the patient can breathe through the larynx and drying will be diminished.

Holinger⁵³ (1944) found that intubation was not successful in his hands since it was followed by chronic laryngeal stenosis. (He did not explain what he meant by chronic laryngeal stenosis. If he implied that the patient became a chronic tube carrier, this has never occurred in my own experience.—Ed.)

Tracheotomy. Most writers on this subject have signified a definite preference for tracheotomy as compared to intubation under any circumstances. Others believe that intubation should be used as a temporary measure before a tracheotomy is performed. A few still feel that intubation has an honorable place in our armamentarium and if used in properly indicated situations will obviate the need for tracheotomy and will reduce morbidity and mortality.

Smith¹⁰² (1919) reported a case of laryngeal edema following influenza which was treated by tracheotomy with recovery. Lynch⁷¹ (1924) reported 5 cases due to *Staph. albus* treated by tracheotomy; all recovered. Clerf²² (1924) described a case in which 17 "life-saving" bronchoscopies

were performed following tracheotomy. He stressed the fact that plugging and not pneumonia was the most important complication. He said that in those cases where there was complete absence of cough after tracheotomy, the patients will die unless the secretions are removed mechanically.

Strachan¹⁰⁶ (1925) reported 3 cases in which intubation tubes were of no help and tracheotomy helped only for a little while. Postmortem examinations showed that all the bronchi were plugged. Dixon³² (1925) reported 1 case in which a tracheotomy was done with recovery. Daily and Allen²⁷ (1926) described the case of an 8 year old boy who required a tracheotomy and recovered. Gittins^{41,43} (1926) cited 14 cases in 10 of which tracheotomy was done; there were 6 deaths. In 1936, out of 32 cases 20 required tracheotomy; 12 of these died—a mortality rate of 60%. Leigh⁶² (1927) advised tracheotomy because he thought intubation would cause ulceration.

Baum³ (1928) stated, "Because of the dryness . . . I have been led to the conclusion that tracheotomy has a tendency to cause too rapid evaporation of secretion increasing the difficulty of expulsion and prolonging the period of dryness with an increased tendency to bronchial plug formation. The direct blast of air coming through the tracheal cannula without the warming and moistening effect of the mucous membrane of the upper respiratory tract seems to predispose to this occurrence." (He does not mention the use of steam or medicated solutions instilled into the tracheal cannula.—Ed.)

Beare¹¹ (1930) writing from Australia said, "Of one thing I am convinced and that is that tracheotomy does not relieve the respiratory distress one iota. This was done on several occasions and no benefit whatever resulted." Myerson⁸⁰ (1930) in a paper describing general observations and experiences with tracheotomy, cited several cases. Thenebe¹⁰⁷ (1932) reported 51 cases of which 24 required tracheotomy; there were 6 deaths—a mortality rate of 25%. He urged early operation, "fearing the consequences of waiting too long." Johnson⁵⁹ (1933) reported 3 cases that were tracheotomized and recovered. He encountered much mucus plugging and advised bronchoscopic suction. Oliver and Turner⁹⁰ (1933) reported 3 cases of acute laryngeal edema complicating measles in which tracheotomy was done; there were 2 deaths.

Neffson and Wishik⁸² (1934) reported 400 cases of laryngeal obstruction. tracheotomy was done in 18 of these—10 died, a mortality rate of 56%; (The general mortality rate of the entire series was 4.8%.) Brennemann *et al.*¹⁵ (1938) concluded, "Tracheotomy is advocated as the procedure of choice unless relief can be obtained from bronchoscopic aspiration alone." Cawthorne²⁰ (1939) gave a good general description of the procedure of tracheotomy. MacCreedy⁷² (1940) advocated early tracheotomy. However, he said, "Where the patients were under constant observation and it has been possible to watch them constantly many have recovered without tracheotomy." Waldapfel¹¹² (1940) advised removal of a segment of tracheal ring cartilage, during tracheotomy. Orton *et al.*⁹¹ (1941) stated, "Tracheotomy is the operation of choice and should be done as soon as possible."

Gilbert *et al.*⁴⁰ (1941), finding a 60% mortality rate (4 deaths out of 6) for intubation, a 50% mortality rate (2 deaths out of 4) for intubation combined with tracheotomy, and a 20% mortality rate (1 death out of 5) for tracheotomy alone, recommended tracheotomy as the operation of choice; in the cases cited there was involvement of the larynx and trachea only. In 8 cases with laryngotracheobronchial involvement there were 7 deaths (2 out of 2 with intubation; 2 out of 2 with intubation and tracheotomy; and 3 out of 4 with tracheotomy alone).

Neffson⁸⁸ (1942) analyzed 126 cases tracheotomized because of acute obstruction of the larynx, trachea and bronchi. These occurred in a series of 1360 cases of laryngeal obstruction over a 10 year period. He found that the incidence of tracheotomy had increased from 5.3 % during the first 7 years to 19.4 % during the last 3 years; the mortality rate of tracheotomy fell from 50 % during the first 7 years to 24.3 % during the last 3 years. The mortality rate for all tracheotomized patients was 35 %; the general mortality rate in the entire group of 1360 cases was 9.5 %. Walsh¹¹³ (1944) found that tracheotomy was required in 35 % of his cases.

Holinger⁵³ (1944) stated that early tracheotomy results in lowered mortality.

Postoperative Care. Postoperative care is the more important part of tracheotomy. The most serious complication has been the formation of mucus plugs producing bronchial obstruction. All efforts in the after-care of a tracheotomy have been directed toward the prevention and removal of these plugs.

Gittins⁴¹ (1926) advised the instillation of "... adrenalin 1:10,000 in saline to soften plugs of secretion which are more troublesome than in true diphtheria." He also urged routine bronchoscopic removal of plugs before they produce obstruction and the use of an oxygen tent.

Richards⁹⁶ (1933) advised instillation of a weak solution of sodium bicarbonate into the trachea, bronchoscopic removal of plugs, a good suction apparatus at the bedside, and specially trained nurses.

Neffson and Wishik⁸² (1934) stated, "Following operation the patient is placed in a cubicle, which is saturated with steam. The foot of the bed is raised in order to provide postural drainage. The tube is covered with several loose layers of gauze kept moist with warm boric acid solution. Several drops of warm 5 % solution of sodium bicarbonate are dropped into the tracheotomy tube every 10 or 15 minutes for the 1st day, then less often, as necessary. Tracheal suction with a soft rubber catheter is performed every $\frac{1}{4}$ or $\frac{1}{2}$ hour for the first 2 days, then when indicated . . . Specially trained nurses are essential for good results."

Galloway³⁸ (1939) advised postural irrigation using 4 to 15 cc. of 3 to 5 % of warm sodium bicarbonate solution dropped into the tracheotomy tube with inspiration and the head elevated. The head is then lowered and suction applied by means of a catheter through the tracheotomy tube.

Cassidy¹⁹ (1939) reported doing 38 bronchoscopies in a single case for the removal of plugs.

Brighton¹⁶ (1940) instilled 1 % ephedrine in normal saline solution and a sterile 5 % sodium bicarbonate solution through the tracheotomy tube.

Holinger *et al.*⁵² (1941) asserted that oxygen increases the viscosity of the tracheobronchial secretions and that carbon dioxide diminishes secretion by stimulating its resorption, liquefies the sputum and stimulates the cough reflex. They maintained that when oxygen is used, both steam and carbon dioxide are necessary to neutralize the drying effect of the oxygen, neither one being sufficient by itself. A concentration of 5 to 10 % of carbon dioxide is used.

Neffson⁸⁸ (1942) described detailed postoperative care and urged the taking of routine roentgenograms of the chest right after tracheotomy in order to detect tension pneumothorax as soon as possible. He cites other complications following tracheotomy such as acidosis and alkalosis, extreme restlessness and convulsions, and prolonged apnea. Various difficulties in decannulation are described.

Walsh¹¹³ (1944) instilled saline solution and neosynephrine or tuamine into the tracheotomy tube.

Baum¹⁰ (1944) advised lavage and aspiration. He found that no solution was especially efficacious as a liquefier.

It is apparent that these cases require assiduous and continuous care to prevent the formation of plugs; once they are formed they are often very difficult to remove and present a serious hazard to life.

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DERMATOLOGY AND SYPHILOLOGY

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GRANULOMA INGUINALE

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GRANULOMA inguinale (venereum) has been known as a disease entity for more than 50 years. In spite of about 20 years intensive study, espe-

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cially in the United States, much confusion still exists regarding this disease, no little of which is occasioned by the great interest in a totally different process designated by a somewhat similar name, lymphogranuloma venereum. Lymphogranuloma venereum was reviewed in this Journal by Beerman, Ingraham and Stokes⁶ in 1939. The following summary, presented in a more or less didactic fashion, gives the essential facts about granuloma inguinale in so far as the recent literature is concerned.

Much credit must be given to certain individuals and groups for their tireless efforts and prolonged study which have led to our better understanding of this disease. Chief among the investigators are the University of Georgia group (Torpin, Sanderson, Pund, Greenblatt, Dienst and Brandt) and the New Orleans workers (D'Aunoy and von Haam). Many others have contributed recently to individual phases of the increasing knowledge of granuloma inguinale (Goldzieher and Peck, Harris, Halty, Williamson, Howard Fox, DeMonbreun, Harry M. Robinson, Schoch and Alexander, Scott, Lyford and Johnson, Paggi and Hull, and numerous others whose work will be specifically referred to).

Definition. Granuloma inguinale is a chronic specific granulomatous infection, manifested clinically by involvement of the skin and subcutaneous tissue, usually of the inguinal region, and histologically by the presence of Donovan bodies within large mononuclear cells. It is auto-inoculable and only feebly transmissible.

Synonyms. Granuloma inguinale has been described under a variety of names: Granuloma venereum, granuloma genito-inguinale, granuloma pudenda tropicum, ulcerating granuloma, sclerosing granuloma, chronic venereal sores, granuloma contagiosa.

Historical Review. The disease was probably first recognized by McLeod⁴⁶ (1892) in India. He described it under the term "serpiginous ulceration of the genitals." Conyers and Daniels¹⁴ (1896) reported cases as a separate clinical entity from British Guiana and gave accurate clinical descriptions of the disease. They named it granuloma inguinale. Gallo-way²⁷ (1897) noted a case in London. Major C. Donovan²² (1904) demonstrated the organism which he found constantly in the lesions of patients suffering from the disease in the Madras General Hospital in India. Later Lynch⁴² (1921) of Charleston isolated and cultured a gram-negative encapsulated bacillus which he felt certain was the Donovan body. Grindon³⁵ reported the first case in the United States in 1913, and in the 1920's numerous cases were reported from all parts of the country (Randall, Small and Belk,⁶² Reed and Wolf,⁶⁴ Gage,²⁶ Johns and Gage,⁴¹ Fox,²⁵ Schochet,⁷⁰ Symmers and Frost⁷⁸). The infectious nature of the process was demonstrated by transmission to monkeys by DeMonbreun and Goodpasture,¹⁸ to human beings by McIntosh⁴¹ (1926) and more recently by Greenblatt and his associates^{19,31} (1938 and 1939). Aragão and Vianna³ of Brazil first introduced tartar emetic into the treatment for granuloma inguinale (1913) and Williamson⁸⁷ (1933) found fuadin highly successful.

Etiology. The identity of the possible causative agent of this disease has occasioned much controversy. From 1882 to 1905 it was thought to be that of tuberculosis or syphilis. Later a symbiotic infection of a spirochete and short motile rods was brought forth as the possible etiology by Butts⁸ (1937). Donovan²² (1904) reported the findings of intracellular organisms, supposedly protozoa, and since his discovery these bodies have been called the Donovan organism; or Donovan bodies. They are constantly associated with the disease, and, though accepted as diagnostic,

have not fulfilled Koch's postulates as to their etiologic rôle. These bodies have been variously interpreted as diplococci (Seibert;⁷² Martini⁴⁸), fungi (schizomycetes, Aragão and Vianna,³ 1913), bacteria related to the *Bacillus mucosus capsulatus* group (Randall, Small and Belk;⁶² Demanche and Lévy-Bruhl;¹⁷ Poindexter⁵⁷), as an organism related to rhinoscleroma (Goodman^{29a}) and the Klebsiella group (D'Aunoy and von Haam¹⁶). Most authorities are in agreement that the Donovan organism, even though it might prove not to be etiologic, is of high diagnostic value in that it is constantly associated with the disease process.

Successful culture was claimed by Aragão and Vianna³ (1913); Flu²⁴ (1911); Goldzieher and Peck²⁸ (1926); McIntosh⁴⁴ (1926-28); Walker⁶⁵ (1918); D'Aunoy and von Haam¹⁶ (1937); Menon and his associates^{47,48,49,50} (1933 and 1935). Dienst, Greenblatt and Sanderson;¹⁹ Greenblatt, Dienst, Pund and Torpin³¹ as well as Carter, Jones and Thomas¹¹ have denied that the true etiologic agent of the disease has been cultured, since the organisms cultured have in most instances failed to reproduce the disease. Anderson² (1943) working with deMonbreun's material, which was rich in Donovan bodies and with remarkably little bacterial contamination, reported the cultivation in the yolk sac of living chick embryos of a microorganism that has all the morphologic characteristics of the Donovan organism and is as yet neither cultivable on ordinary culture media nor pathogenic for mice, dogs or monkeys.

Successful transmission of the disease to animals has been reported by Menon and Annamalai,⁴⁸ deMonbreun and Goodpasture,¹⁸ Goldzieher and Peck,²⁸ but denied by Campbell⁹ and the University of Georgia group (Dienst, Greenblatt and Sanderson¹⁹), who were unable to transmit the disease to rabbits, guinea pigs, rats and mice by intraperitoneal, intratesticular or subcutaneous inoculation of material aspirated from unruptured pseudobuboes. The Georgia group^{19,20,30,31,32,33,69} (1938-39) has reproduced the disease in humans by inoculation of aspirated pus from pseudobuboes of granuloma inguinale which contained no other organisms than Donovan bodies. These organisms were recovered in abundance, to the exclusion of other organisms, from the experimentally-induced lesions. The workers conclude that the Donovan bodies are strictly tissue parasites to man (Greenblatt³⁰) (1943).

The organism is successfully stained by the Wright or Giemsa and by Delafield's hematoxylin method with eosin, and by silver (Dieterle²¹) impregnation method. It is characteristically seen within large mononuclear endothelial cells, has an affinity for hematoxylin, and is gram-negative. In acute fulminating lesions or in the immature stages of the development of the organism, it is not encapsulated, but acquires this with age (Sanderson⁶⁹). The nucleus of the encapsulated body resembles a small curved bacillus and shows one or two terminal swellings simulating polar bodies, and may appear diplococcoid. Atypical forms with diphtheroid structure or appearing as non-encapsulated bacillary or diplococcoid forms surrounded by a zone of rarefaction are frequently seen. Varying interpretations of the organism's nature may be easily explained by this pleomorphism. In sections the affinity of the intracytic bodies for silver salt is characteristic, and they stain black to brown with a closed safety-pin appearance because of their elongated, ovoid and intensified polar staining reaction.

Recently Mortara and Dienst⁵¹ (1943) reported a new method to demonstrate Donovan bodies in exudate from patients with granuloma inguinale. It is not proposed to replace Wright's stain, but is to be used in conjunc-

tion with it in doubtful cases. The new procedure demonstrates added characteristics of the Donovan body that further differentiate it from the *Klebsiella* group of bacteria. The authors obtained best results with the following procedure:

1. Fix smear of exudate by drying in air or gentle heating.
2. Flood smear with basic fuchsin (0.5% aqueous solution) 2 minutes.
3. Wash off excess dye with water and decolorize with citric acid (0.5% aqueous solution) until dye ceases to leave the smear (approximately 5 seconds).
4. Wash in water and counterstain with aniline blue (1% aqueous solution, 1 minute). (Aniline Blue, water soluble C. I. No. 707, National Aniline & Chemical Co.)
5. Wash, dry and examine with oil immersion lens.

If this procedure is used in dry smears from lesions of granuloma inguinale the intracellular microorganisms are stained a deep pink and the endothelial cell is stained deep blue. Extracellular Donovan bodies are also stained pink with a delicate blue outer covering. The miscellaneous bacteria and spirochetes that may be present are stained blue. Desquamated epithelial cells are not usually decolorized and remain pink. Encapsulated *K. pneumoniae* is stained blue by this method.

The difficulty many experience in getting positive smears may be overcome by the suggestion of Weidman⁸⁶ that "there is a trick in staining for the Donovan body. When differentiating the Giemsa (or other Romanowsky) stain do not let it remain too long in the water. After staining, slide it into the water and then out promptly; otherwise the capsule becomes bleached and the Donovan body cannot be distinguished from the diplococci."

Alexander and Schoch¹ (1940) were successful in using the Giemsa stain to demonstrate the typical pathologic findings in granuloma inguinale. They conclude that it is necessary for the demonstration of the pathognomonic histologic picture of granuloma inguinale.

Geographic Incidence. The geographic distribution of the disease is wide and includes India, southern China, Australia, West Africa, the East and West Indies and most parts of North, Central and South America. Like lymphogranuloma venereum, it was formerly regarded as a tropical disease, but this is hardly a tenable view today in that cases have been noted from practically all parts of the United States. Greenblatt³⁰ (1943) points out that cases have been reported from almost every country and zone, from the equator to Scandinavia. As indicated by Fox²⁵ the number of cases reported does not give a fair idea of the prevalence of the disease in the United States. D'Aunoy and von Haam¹⁶ (1937), also, cite numerous case reports from the literature showing the wide distribution of granuloma inguinale in the United States and believe that the reported cases are not indicative of the true incidence of this infection in the United States. Harris³⁹ (1930) states that the disease has been noted in this country "from Boston to San Francisco; from Portland to Savannah; as far north as Wisconsin and as far south as Georgia and New Orleans." He believes that the disease seems to travel from large seaports towards the inland sections along the great waterways.

Epidemiology. The infrequency of infection of the coital partner has led some to doubt the venereal origin of granuloma inguinale (Campbell,⁹ 1928). In fact, undoubted examples of non-venereal infection with granuloma inguinale have been reported (Sidlick,⁷⁶ 1927; Campbell,⁹ 1927).

Some authors have suggested the possibility of insect vector transmission. It is a relatively uncommon disease because of the difficulties of transmission. Most cases appear during the period of active sex life, but the disease has been reported in a newborn baby (Arnell and Potekin⁴); in children of 2 to 6 years of age (McLean,⁴⁵ 1911; Sabella and Wise⁶⁸), and in an old man (94 years of age) (D'Aunoy and von Haam,¹⁶ 1937). In the United States, negroes are affected more than whites. D'Aunoy and von Haam¹⁶ found a ratio of 10:1 in their series of 294 cases from New Orleans. Greenblatt³⁰ (1943) states that of some 75 cases studied in the University of Georgia in 8 years, Donovan bodies were found in only 3 white patients. In 1 of these, the lesion was on the vulva, was self-limited and healed without therapy. Hindus are affected more frequently than Mohammedans. Thus, Menon⁴⁷ (1933) and Nair and Pandalarai⁶⁴ (1934) have independently and from different sources in India reported the incidence of Hindu to Mohammedan to be 72 to 1 and 57 to 4, respectively.

Although it is generally believed that women are more often the victims of granuloma inguinale than men (Galloway;²⁷ Grindon³⁵), D'Aunoy and von Haam found that men are affected twice as often as women. This is confirmed by other series of cases in the literature (Harris,³⁹ Fox²⁵). It is possible that infections in women may have escaped notice because so many lesions are located on the vagina and cervix, while in the male the lesions are more conspicuous and disturbing.

Pathologic Histology. Although descriptions of the clinical processes produced by granuloma inguinale are varied, there is certain unanimity of opinion concerning the histologic changes which permit specific diagnosis from clinically suspected lesions. According to Pund and Greenblatt⁵⁹ (1937) the essential features histologically are: massive granulation tissue with numerous plasma cells, scanty lymphocytes, and scattered polymorphonuclear leukocytes with miliary collections in the papillae, pseudo-epitheliomatous hyperplasia of the epidermis, and a pathognomonic, mononuclear cell (endothelial cell? von Haam,^{84b} 1940). This cell, which permits certain histologic diagnosis, is large (25 to 90 microns in diameter), has intracytoplasmic cysts filled with deeply stained rod-like or round bodies which have an affinity for silver salts, which color them black or brown and give them a closed safety-pin appearance because of their elongated, ovoid, and intense bipolar staining reaction. von Haam and D'Aunoy^{16, 84} state that the histology of acute granuloma venereum is a non-specific highly vascular granulation tissue which follows a brief preliminary stage of subcutaneous infiltration and which has no characteristic appearance. In the chronic hypertrophic lesions, there is a massive development of collagenous tissue surrounding nests of plasma cells and lymphocytes.

Pathogenesis. Traditional teaching has repeatedly emphasized that granuloma inguinale is a disease of the skin and corium, and not of the lymphatics (*cf.* lymphogranuloma venereum).^{*} The frequent inguinal location of the process, which is often preceded by a primary focus on the genitalia, led Greenblatt and his co-workers to suggest that the Donovan body spreads from an inconspicuous primary focus by way of the lymphatic system to the lymph nodes, where a temporary though mild inflammatory focal reaction with perilymphadenitis occurs. During this process, the

^{*} Sobel and Pensky have recently reported a case of granuloma inguinale involving the lymphatics (bubonulus). (Sobel, N., and Pensky, N.: Arch. Dermat. and Syph., 48, 494, 1943.)

Donovan body reaches the papillæ and corium of the overlying skin, where an inflammatory reaction is produced. The reaction may be subacute or chronic. In 2 cases, removal of lymph nodes underneath extensive granulomatous involvement with this disease showed involvement of the lymph nodes to substantiate their viewpoint.

Location. The majority of cases occur in the inguinal region, on the external genitalia, perineum and perianal region, and to a lesser extent on the cervix,^{55,59b,60} urethra, uterus,⁵⁸ tubes,⁵⁸ ovary,⁵⁸ bladder, and rectum.^{5,15,16} Extragenital involvement occurs in about 6% of the cases (Greenblatt, Torpin and Pund,³³ 1938^{16,25,63,76}) and includes the mouth,^{16,33-36,40,52,56,67,73,77,79} face (cheek, nose),^{42,67*} neck,^{16,33,42,56,67} throat,^{40,67} larynx and pharynx,^{16,33,40} back of the hand,¹² and thigh.⁷³ It has occurred at the site of a skin graft.²⁶ Infection of the gastrointestinal tract, of the bones,^{55,71} and other viscera has also been reported, but is rare. Stricture may follow involvement of the anal canal (Crane and Kimball,¹⁵ D'Aunoy and von Haam,¹⁶ 1937; Ault⁵), and rarely the process extends into the colon (Crane and Kimball¹⁵).

The incubation period of granuloma inguinale has been variously recorded from 2 days to 3 months. Greenblatt and his co-workers^{19,20,30,31,32,33,69} reported an incubation period of about 21 days in experimental human inoculation, although the exact time was difficult to determine.

We propose the following adaptation of Halty's³⁷ classification and description of clinical symptoms:

1. *The nodular form* begins as an elevated nodule 1 to 4 cm. in diameter, is reddish in color and soft in consistency and grows to a variable size. It is usually an early manifestation and in most cases will undergo further changes, but may regress with or without treatment. Greenblatt and his co-workers³⁰ (1943) suggest the term "pseudobubo" for this subcutaneous nodular involvement.

2. *The ulcerovegetative form* is the most common clinical variety. It develops from the nodular type by excoriation or maceration of the superficial epithelium followed by the development of a rather spongy and easily bleeding surface covered with granulation tissue. The lesion spreads peripherally by continuity or new lesions may appear as the result of autoinoculation. In the earlier stages the granulation tissue is clean, pinkish red, the discharge serosanguineous, and the surface relatively smooth, whereas in older lesions or in grossly neglected cases, the surface becomes more uneven, the discharge seropurulent and foul smelling, and the granulation tissue changes to a grayish dirty hue. The border is sharply demarcated, indurated, and raised above the level of the skin. The process shows frequent tendency to spread along the inguinal creases and progresses slowly over weeks and months. This stage has given the disease its name. When healing takes place, atrophic depigmented scars develop with permanent loss of hair. Sometimes contact ulcers may occur in which, in the natural state, the ulcerated areas appose and are in contact with each other (Torpin, Sanderson and Brandt⁸³, 1939).

Secondary infection, particularly with spirochetes or aerobic or anaerobic organisms may considerably alter the picture and result in the production of deep ulceration and necrosis of the soft tissue. If a serpiginous ulcer develops on the penis, marked mutilation may result, for spread on the mucous membrane of a genital organ is more rapid than on the skin. In 55 cases of their series, D'Aunoy and von Haam¹⁶ (1937) noted exten-

* Weiner and co-workers have reported granuloma inguinale of the eyelid. (Weiner, A. L., Gaynon, I. E., and Osherwitz, M. S.: *Am. J. Ophthalm.*, 26, 13, 1943.)

sive necrosis of the deeper layers of the soft tissue, and particularly in colored women, extension into the rectovaginal septum with the production of rectovaginal fistulae and perianal phlegmon. This secondary infection is usually ushered in with fever and general malaise. The usual history is that the lesion "took a sudden turn for the worse." Two patients so afflicted died, and at autopsy were found to have far-reaching cellulitis of the soft parts of the pelvis with far-advanced pyelonephritis in association with genital mutilation. Cardwell and Pund¹⁰ record the development of carcinoma superimposed on a chronic granuloma inguinale of the cervix. Wilson⁸⁸ noted that under the influence of pregnancy the disease progressed rapidly and that these patients seemed to have a tendency to stillbirths or neonatal deaths higher than the average individual.

3. *Hypertrophic lesions* are not frequently seen. Halty³⁷ states that this type is distinguished by the exaggeration of the proliferative reaction. Large vegetating masses, sometimes several centimeters high, spring from the lesions simulating simple vegetation or more rarely neoplasm. These masses present a cerebriform surface with considerable debris and the discharge has a markedly fetid odor.

Elephantiasic form: Esthiomene-like pictures are now being recognized with increasing frequency as being due to granuloma inguinale, as well as lymphogranuloma venereum (D'Aunoy and von Haam;¹⁶ Alexander and Schoch;¹ Fox²⁵). This type varies from mildly hypertrophic ulceration to true elephantiasis with deep ulceration. In a differential diagnosis from lymphogranuloma venereum, D'Aunoy and von Haam¹⁶ point out that in granuloma inguinale the swelling is associated with extensive scar formation in or around the enlarged tissue part indicating previous ulceration, whereas in lymphogranuloma venereum the skin is thick and edematous, but otherwise normal.

4. *The cicatricial type* is the result of a peculiar host reaction to the infectious agent leading to the formation of keloid-like lesions. The surface of the lesion may be compared to the relief map of a mountainous country with depressions between knobs of piled up tissue. The lesion is firm and elastic and the overlying skin may or may not show scars of previous ulceration. This keloid is not a healing or healed stage of the disease, but is a progressive lesion, since puncture will reveal the Donovan bodies and histologic examination will show small nests of inflammatory cells containing the organism embedded in dense collagenous fibrous tissue. In older cases, Cole¹³ noted a tendency to cicatrization with lymphatic obstruction, which resulted in marked changes in the labia and the formation of a Hottentot apron of the clitoris.

Systemic symptoms are usually slight or absent unless there is secondary infection, deep ulceration, rectal stricture or extension of the process to the tubes or ovaries. D'Aunoy and von Haam¹⁶ in their series noted slight discomfort, heavy discharge, itching, burning pain, urinary and rectal complaints, weakness and fever. Paggi and Hull's⁵⁵ case of metastatic granuloma venereum had very severe constitutional symptoms. In our own experience, symptoms vary from practically nothing to such severe excruciating pain that walking becomes practically impossible. Extensive ulceration may actually lead to death (Greenblatt,³⁰ 1943).

Complications. Granuloma inguinale may be associated with or complicated by other venereal disease. Shropshear and Hibbs⁷⁵ (1941) noted that 3 out of 7 cases of granuloma inguinale in the male, observed during the year previous to publication, were complicated by gonorrhea. Fusospirochetosis is a frequent complication of granuloma inguinale, and

syphilis, chancroid and lymphogranuloma venereum may be coëxistent. Occasionally malignancy may be superimposed (Greenblatt,³⁰ 1943).

Diagnosis. In 1926, Goldzieher and Peck²⁸ used a complement fixation test antigen from excised tissue intracutaneously injected, and scratch tests which seemed to be specific for granuloma venereum, but others (Halty,³⁷ D'Aunoy and von Haam¹⁶) deny the specificity of any serologic, allergic, or other immune reaction so far proposed. Taussig and Somogyi⁸⁰ found hyperglobulinemia in 7 cases which were examined for this. The euglobulin percentage was extremely high. This is not characteristic of the disease (*cf.* lymphogranuloma venereum). The formol gel reaction skin tests and animal inoculation are of no value in the diagnosis of granuloma inguinale (von Haam,^{84a} 1938).

Diagnosis clinically is usually based upon the presenting symptoms and the identification of the Donovan bodies in smears or in tissues in association with the appearance of the "pathognomonic cell." Our routine consists of the performance of a biopsy, dividing the specimen into 2 parts, one for pathologic study, the other for smears from the deeper surfaces of the specimen, where the organisms are likely to appear more abundantly than on the surface. Giemsa or Wright stains are used for the smears, but staining with silver salts gives a characteristic closed safety-pin appearance to the organisms.

Torpin, Greenblatt and Pund⁸² (1939) state that a "successful way fully to diagnose each case is to carry out the following routine, much of which is laboratory in nature: (1) Repeated Wassermann or Kahn tests to rule out syphilis; nigrosine stain²⁰ or darkfield study for *Treponema pallidum* and other spirochetes. (2) Smears stained for gonococci, Donovan bodies, fusospirochetes, Ducrey bacilli, yeast, etc. (3) Chancroid intradermal tests.³² (4) Frei test. (5) Biopsy for Donovan bodies in tissue section, since not infrequently it is difficult to demonstrate these bodies in smears because of marked contamination by other organisms. The biopsy will establish the diagnosis in such cases and at the same time rule out tuberculosis, carcinoma, etc. To facilitate the diagnosis, all buboes, including the pseudo-bubo of this condition, should be aspirated under sterile conditions and routine smears and cultures made."

Treatment. For rational therapy, definite early diagnosis not only of granuloma venereum but of complications or concomitant venereal diseases must be made and proper treatment instituted. A number of methods of both local and general treatment have been proposed for granuloma venereum. All treatment methods leave a certain residue of unsuccessful cases, which by skillful combination of these methods may result in cure. Torpin and his co-workers⁸² recommend 10% neoarsphenamine in equal parts of glycerin and cod-liver oil as an excellent local application to check phagedenic effects of fusospirochetosis as well as to serve as prophylaxis against such contaminants. They recommend in addition a local anesthetic such as Nupercain for its analgesic effect. Sodium perborate, potassium permanganate, tartar emetic soaks 1:1000 or a 1% tartar emetic ointment (Manson-Bahr) have been used locally.

The local use of a mixture of 20% resin of podophyllum in olive oil yielded complete cures in 102 patients treated by Tomskey, Vickery and Getzoff⁸¹ (1942). The drug probably acts as a dehydrating agent and also has some cauterizing effect. Its use not only lessened hospital stay considerably (35%) but also the favorable response was more than twice that of those who were also treated with antimony and potassium tartrate. In treatment, secondary infection should be eliminated by cleansing the

lesion with hydrogen peroxide and hot sitz baths twice a day. The 20% resin of podophyllum in olive oil is applied to the lesion after each bath, for 5 to 7 days. Local topical analgesics are recommended for any resultant burning or pain, applied about 10 minutes before the resin of podophyllum. When the exuberant granulations have disappeared and a healthy base is evident, resin of podophyllum is discontinued and scarlet red ointment is applied following each bath to stimulate epithelization. The application of resin of podophyllum to any small resistant areas should be continued if a complete cure is to be obtained.

Potassium and antimony tartrate (tartar emetic) has been the standard method of treatment since its introduction by Aragão and Vianna³ in 1913. It is given intravenously beginning with 1 to 2 cc. and gradually increasing the total dose to 10 to 15 cc. depending upon tolerance. Our experience with drug indicates that response to treatment, if it is going to occur at all, will be manifested by 2 to 3 months of treatment, at which time, if no obvious healing takes place, change of regimen should be made. Some writers caution against more than a 20 to 30 injection course, although we have not found any increase in toxicity in the continuous use of the drug for 50 to 60 injections. Toxic reactions consist of nausea, vomiting, diarrhea, arthralgia, myalgia, coughing or sneezing attacks, and occasional nitritoid reactions, and nervous spasm.

Fuadin, named after Fuad I, late King of Egypt, an intramuscularly administered antimony compound, was introduced into the treatment of granuloma inguinale by Williamson and co-workers⁸⁷ in 1933, following their observation of its remarkable efficacy in the treatment of bilharziasis. The compound was originally devised by Khlil, and is sodium antimony iii biscatechol disulfonate of sodium. Fuadin can be used in cases in which tartar emetic cannot be tolerated because of reaction, or in cases in which tartar emetic has failed. Williamson and co-workers recommend a 7% solution with dose beginning with about 1.5 cc. and gradually being increased every 1 to 2 days up to 5 cc. intramuscularly. They reported 14 cases with excellent results superior to those obtained with tartar emetic. Rajam⁶¹ (1934) considered it effective and more toxic. Shattuck, Little and Coughlin⁷⁴ found sodium antimony thioglycollate and antimony thioglycolic acid effective drugs. Anthiomaline (lithium antimonio-thiomalate) has also been tried (Robertson and Sharp⁶⁵). Hanschell³⁸ reports the enhancement of the antimony effect by combining its use with fever therapy, Nair and Pandalai⁵⁴ by non-specific therapy, and Earle³³ by the combination of Fuadin and sulfanilamide. Treatment should be continued for at least 2 months after complete healing in order to avoid relapse, which is unfortunately too prone to occur. Favorable response to chemotherapeutic agents is roughly inversely proportional to the duration of this infection, although at times surprisingly good results are obtained in long-standing cases (cf. Brandt and Gatewood⁷).

In the event of failure of chemotherapeutic agents, physical and surgical methods may have to be employed. Preliminary roentgen ray irradiation may be followed by electrosurgical excision and further roentgen ray treatment. Greenwood³⁴ in an analysis of 22 cases states that fulguration of the edges of the advancing border of the lesion plus cleanliness resulted in complete healing of all cases within 70 days. Murray⁵³ reports the successful use of ultraviolet irradiation. Robinson and co-workers⁶⁶ (1942) propose surgery for many cases previously considered hopeless. Their results are in some cases truly amazing.

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BOOK REVIEWS AND NOTICES

NEW BOOKS

- Annual Review of Biochemistry.* By JAMES MURRAY LUCK, Editor, Stanford Univ., and JAMES H. C. SMITH, Associate Editor, Carnegie Institution of Washington, Division of Plant Biology, Stanford Univ., California. Vol. 13. Pp. 795. California: Stanford Univ. P. O., Annual Reviews, Inc., 1944. Price, \$5.00.
- X-ray Examination of the Stomach.* A Description of the Roentgenologic Anatomy, Physiology, and Pathology of the Esophagus, Stomach, and Duodenum. By FREDERIC E. TEMPLETON, M.D., Head of the Dept. of Roentgenology, The Cleveland Clinic. Formerly Associate Professor of Roentgenology at the Univ. of Chicago. Pp. 516; 297 figs. Chicago: Univ. of Chicago Press, 1944. Price, \$10.00.
- Medical Clinics of North America.* The Mayo Clinic Number. Symposium on Chemotherapy. By 36 Contributors. Pp. 789-1028; 75 figs. Philadelphia and London, Saunders, 1944. Price, \$16.00 per year.
- A Source-book of Biological Names and Terms.* By EDMUND C. JAEGER, Riverside Junior Coll., Riverside, Calif. Pp. 256. Springfield, Ill.: Thomas, 1944. Price, \$3.50.
- Surgical Disorders of the Chest.* Diagnosis and Treatment. By J. K. DONALDSON, B.S., M.D., F.A.C.S., MAJOR, M.C., A.U.S.; Diplomate, American Board of Surgery; Associate Professor of Surgery and in charge of Thoracic Surgery, Univ. of Arkansas School of Medicine, etc.; Surgical Staff, St. Vincent's Infirmary, and Visiting Staff, Baptist Hospital, Little Rock, Ark. Formerly Chest Surgeon to Arkansas State Hospital for Nervous Diseases; Associate Surgeon, Robert B. Green Hospital, Visiting Surgeon to Santa Rosa, Nix, and Medical Arts Hospitals, San Antonio, Texas. Pp. 364; 127 figs. Philadelphia: Lea & Febiger, 1944. Price, \$6.50.
- Minor Surgery.* Edited by HUMPHRY ROLLESTON and ALAN MONCRIEFF. Pp. 174. New York: Philosophical Library, 1944. Price, \$5.00.
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- The Gastro-intestinal Tract.* A Handbook of Roentgen Diagnosis. By FRED JENNER HODGES, B.S., M.D., Professor of Roentgenology, Univ. of Michigan, Medical School, Ann Arbor, Mich. Pp. 320; numerous illustrations. Chicago: Year Book Publishers, 1944. Price, \$5.50.
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The Practice of Medicine. By JONATHAN CAMPBELL MEAKINS, M.D., LL.D. Fourth Ed. St. Louis: Mosby, 1944. Price, \$10.00.

In this Fourth edition of this widely used textbook of medicine the author considers many of the changes in concept and treatment of disease developed during the war years. A brief discussion of the history and use of penicillin is given. The sections dealing with virus pneumonia, traumatic shock, crush syndrome, immersion foot, and epidemic hepatitis are among several that have been rewritten or are included for the first time. In spite of the shortage of materials the publishers have maintained their high standard of printing. Most of the colored illustrations, with a few notable exceptions, could be omitted with little loss to the reader.

H. S.

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ORIGINAL ARTICLES

THIOURACIL IN THE TREATMENT OF THYROTOXICOSIS CLINICAL EXPERIENCE WITH 37 CASES

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IN 1943 Mackenzie and Mackenzie,⁵ and Astwood and his associates¹ first reported in detail the striking effects of thiourea and related compounds upon the structure and function of the thyroid gland in lower animals. Since that time much additional experimental work with these substances in lower animals has been reported.⁴ Thiourea and its related compound, 2-thiouracil, inhibit the synthesis of the thyroid hormone, probably by affecting an enzyme system in the gland which normally aids in the conversion of iodine into the completed hormone.⁴ When the extrathyroidal thyroid hormone has been destroyed or excreted, a state of thyroid failure supervenes; this cannot be prevented or corrected by iodine, but can be counteracted by thyroxine. The thyroid gland becomes hyperplastic and enlarged, probably because of continued excessive stimulation by the thyrotropic hormone of the anterior pituitary. These characteristic effects cannot be produced in the absence of the pituitary.

The clinical use of thiouracil was first reported by Astwood in 1943,² and a number of additional clinical reports have appeared subsequently.^{3,8,11} The normal human thyroid appears to be resistant to thiouracil and its function seems to be affected, if at all, only after prolonged administration. The drug exerts a marked effect upon the toxic human thyroid gland. Within 1 to 3 weeks after the daily oral ingestion of 0.2 to 1 gm. of thiouracil is begun, most of the manifestations of the disease begin to diminish. There is a decline in the basal metabolic rate and the heart rate, gain in weight, and general subjective improvement. The thyroid enlargement does not always subside, and may actually increase for a time; exophthalmos seldom

recedes.* A rise in the total serum cholesterol often occurs. The development of positive nitrogen, calcium and phosphorus balances has been reported.⁹ Thiouracil has been employed both as a pre-operative agent and in the prolonged treatment of thyrotoxicosis. It is partially destroyed in the intestinal tract and is excreted entirely in the urine. A number of toxic effects have been reported; these include neutropenia, various dermatoses, thrombocytopenia with purpura, jaundice, pharyngitis, myalgia, hematuria, diarrhea, chills and fever.^{3,6,11}

TABLE 1.—COLOR, AGE, SEX, DISTRIBUTION

<i>Color—</i>						
White						33
Negro						4
<i>Age in decades</i>						
	2	3	4	5	6	7
	1	10	8	6	4	3
<i>Sex distribution—</i>						
Male						6
Female						31

TABLE 2.—TYPE OF GOITER, PREVIOUS THERAPY AND DURATION OF SYMPTOMS

<i>Type of goiter—</i>		
Nodular		2
Diffuse		29
Recurrent postoperative		5
Unclassified		1
<i>Previous therapy—</i>		
Iodine alone		4
Iodine and Roentgen ray		5
Thyroidectomy		5
<i>Duration of symptoms—</i>		
Under 6 months		17
Over 6 months		20

TABLE 3.—COMPLICATIONS OF THYROTOXICOSIS

Auricular fibrillation	4
Congestive heart failure	2
Ophthalmopathy	1
Myasthenia gravis	1
Psychoneurosis	1
Mitral stenosis and pregnancy	1
Diabetes mellitus and rheumatic heart disease	1

Material. This report describes our clinical experiences with 37 thyrotoxic patients treated with 2-thiouracil. We have been especially interested in the effects of such therapy when continued over protracted periods of time. In addition we have had the opportunity of examining necropsy material from a thyrotoxic patient who was prepared for thyroidectomy with thiouracil. Our observations also include ballistocardiographic data obtained in 9 thyrotoxic patients before, and at varying periods after thiouracil was begun. In Tables 1, 2 and 3 are presented clinical data pertaining to the patients receiving treatment. We have included in this group 1 patient whose treatment had to be stopped before its effect could be evaluated; she is included because she showed a marked neutropenic reaction associated with fever

* Astwood (Thiouracil Treatment in Hyperthyroidism, J. Clin. Endocrinol., 4, 229, 1944) has recently reported that thiouracil therapy is often followed by apparent regression of exophthalmos, but our observations do not support this view.

and pharyngitis (*vide infra*). With one possible exception, Case 8 below, all of our patients presented unquestionable evidence of thyrotoxicosis. The initial basal metabolic rate was +20% or more in all except 1 patient, a woman who developed recurrent thyrotoxicosis following the removal of a large intrathoracic goiter. Her basal metabolic rate was only +12% before the institution of thiouracil therapy; but in other respects she presented the typical picture of thyrotoxicosis. Among the 30 patients with diffuse toxic goiter the enlargement was marked and firm in 3. The others presented moderate or slight diffuse goiter. With respect to the duration of symptoms our patients have arbitrarily been divided into two groups, depending upon whether their symptoms had been noted for more or less than 6 months. Evaluation of duration of symptoms in thyrotoxicosis is often difficult since the disease is frequently insidious in onset, and even severely toxic patients occasionally deny consciousness of all symptoms. Of the 5 patients showing recurrent postoperative thyrotoxicosis, 4 had previously been operated upon for toxic diffuse goiter; 1 had had a right hemithyroidectomy for a large nodular intrathoracic goiter.

TABLE 4.—RESPONSE TO TREATMENT

General response to treatment—

Complete response	30
Partial response	4
Failures	2
Unclassified	1
Relapsing after withdrawal of thiouracil	10
Relapsing when dosage was reduced	3
Sustained remission when drug stopped	8
Sustained remission when drug reduced	3

Specific response—

Rise in cholesterol	17
Effect on exophthalmos:	
Reduced	4
Increased	2
No change	11
Effect on goiter:	
Reduced	4
Increased	5
No change	27

Results of Treatment. In Table 4 are presented data pertaining to the effects of thiouracil therapy in our patients. It will be seen that 30 (81%) of the patients showed a definitely favorable response to thiouracil, which was reflected by a progressive fall in the basal metabolic rate to normal levels or below, usually associated with concomitant decline in heart rate, gain in weight and general subjective improvement. Four patients (10.9%) showed partial, but not completely satisfactory, improvement; 2 patients (5.4%) failed completely to respond to the drug. In 1 case, referred to above, thiouracil therapy had to be stopped before its results could be evaluated. Among the 30 patients showing a favorable response, 11 remained ambulatory throughout their treatment; the remainder were hospitalized for periods varying from 1 to 3 weeks at the beginning of treatment. The basal metabolic rate was determined at weekly intervals until normal levels were attained, and thereafter at intervals of 2 to 4 weeks. The time required for the basal metabolic rate to fall to +15% or below varied from 5 days to 34 weeks, the average being about 2 weeks. In 6 patients whose initial basal metabolic rates were +50% or higher, the average duration of thiouracil therapy before

the basal metabolic rate fell to $+15\%$ or below was 3+ weeks. Five of these patients were hospitalized during the early part of their treatment. The average period of therapy required to bring about a fall in the basal metabolic rate to $+15\%$ or below in 22 patients whose basal metabolic rates were below $+50\%$ was $2\frac{1}{2}$ weeks. Of these patients 12 were hospitalized during the early part of treatment. Subjective improvement became manifest in from 1 to 12 weeks in the entire group, the average time being $2\frac{1}{2}$ weeks. Three patients who had responded favorably showed definite evidence of relapse when the daily dose of thiouracil was reduced to 0.2 gm. or less, and 10 patients relapsed when the drug was completely withdrawn. Evidence of relapse appeared in from 1 to 4 weeks in these cases and was manifested by a rise in the basal metabolic rate and heart rate, as well as by recurrence of subjective phenomena. All patients who relapsed, however promptly responded when thiouracil was again given in daily doses of 0.4 to 1 gm. Three of these 10 patients have subsequently remained well for periods varying from 1 to 4 months following the complete withdrawal of thiouracil. One patient relapsed on 3 separate occasions when the drug was stopped, responding each time to renewed therapy. She finally elected thyroidectomy and was operated upon, following preoperative iodization, with a good result. Three patients have remained in remission for periods of time varying from 2 to 3 months upon daily doses of thiouracil of from 0.1 to 0.2 gm. Eight patients have remained in remission from 3 weeks to 7 months after complete withdrawal of therapy. Data pertaining to the duration of observation and dosage of thiouracil in 24 cases are shown in Figure 1.

In most cases thiouracil was given in doses of 0.6 gm. daily, in 3 divided doses, for 3 or 4 days. If no untoward reaction appeared the daily dose was then increased to 0.8 or 1 gm., given in 4 or 5 doses. A maximum daily dose of 1 gm. was then maintained until definite evidence of remission appeared, or until it became apparent that no favorable response could be expected. A maximum daily dose of 2 gm. was employed in 2 cases. When a complete remission was indicated by persistence of normal basal metabolic rate and heart rate for about 1 week, the daily dose was gradually reduced to 0.2 or 0.1 gm. When evidence of remission continued for 1 month on this dosage, the drug was usually withdrawn in an effort to determine whether the patient would remain well without medication. Adjuvant treatment consisted of phenobarbital or other sedatives, and various mixed vitamins. One patient, described below, also received irradiation to the pituitary and estrogenic substance by mouth in an effort to inhibit anterior pituitary activity.

In 10 patients estimates of the cardiac output per minute were made, using the ballistocardiographic method of Starr.¹⁰ These determinations were made before treatment and were repeated at periods varying from 12 to 30 days after therapy was begun. In Table 5 are shown percentile changes in cardiac output in 9 of these patients, with percentile changes in their basal metabolic rates determined at

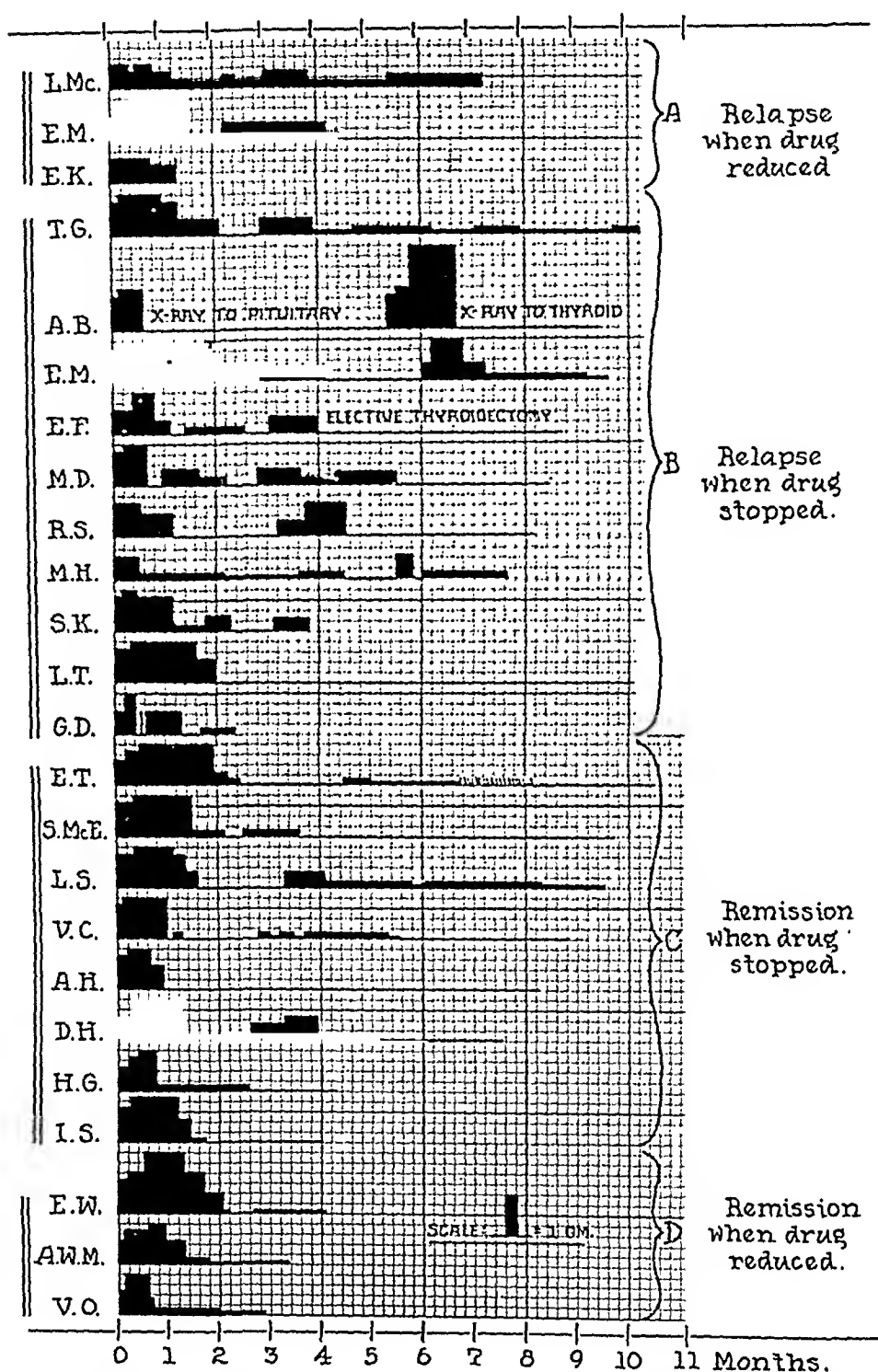


FIG. 1.—Dosage of thiouracil and duration of observation in 24 thyrotoxic patients: A, Cases showing relapse when dose was reduced; B, cases showing relapse when drug was stopped; C, cases showing remission when drug was stopped; D, cases showing remission when dose was reduced.

similar time intervals. In 1 patient, aged 13, cardiac output could not be calculated because of lack of normal standards for comparison, although the tracings indicated a reduction in the degree of hyperkalemia. It will be seen that the cardiac output was reduced in 8 patients coincidentally with the fall in basal metabolism which occurred during treatment. One patient (C. K.), who showed a normal cardiac output but an increased basal metabolism before treatment, had received iodine for several months until 3 weeks before institution of thiouracil therapy.

TABLE 5.—COMPARISON OF CHANGES IN BASAL METABOLISM WITH CHANGES IN CARDIAC OUTPUT, MEASURED BY BALLISTOCARDIOGRAM IN 9 PATIENTS DURING TREATMENT

Patient	Percentile change in B.M.R.	Percentile change in cardiac output	Time interval in days
1. D. M.	-17	-21	30
2. C. K.*	-25	-23	17
3. V. McC.†	-10	-23	23
4. V. O.	-8	-26	17
5. W. B.	-42	-86	26
6. J. M.	-34	+ 3	19
7. E. W.	-17	-44	28
8. H. C.	-37	-42	14
9. P. N.	-43	-30	15

* Cardiac output within normal limits prior to treatment.

† Received thiouracil 14 of the 23 days.

Thiouracil as a Preoperative Agent. Although our chief interest is centered upon the results of protracted therapy with thiouracil, we have employed it as a substitute for iodine in the preparation of 4 thyrotoxic patients for subtotal thyroidectomy. Three of these patients had diffuse toxic goiters and 1 had a toxic nodular goiter which had precipitated congestive heart failure. One patient, discussed below, died 20 hours after operation, but we do not believe that thiouracil contributed to his death. The other 3 patients responded satisfactorily to the preoperative use of the drug, and their postoperative courses were uneventful. In these patients the period of hospitalization from the beginning of thiouracil therapy to the time of operation was 17, 21 and 38 days, respectively. Their basal metabolic rates fell to +15% or below in 8, 14 and 31 days, respectively, after treatment was begun. One of these patients had taken iodine for 4 months before entering the hospital.

At operation the gross appearance of the thyroid glands in these patients differed markedly from that seen in patients treated preoperatively with iodine. There had been no apparent reduction in size of the goiter, and the glands were friable, vascular and bled rather freely. Histologic examination of the tissue in the 3 patients with toxic diffuse goiter showed a complete absence of the usual changes produced by iodine. Instead of the increase in colloid content and flattening of the acinar epithelium, there was marked, persistent hyperplasia, and the appearance was quite similar to that of the untreated toxic thyroid. The nodular goiter removed from the 4th patient presented no histologic evidence of toxicity, and contained

normal amounts of colloid, although the patient was clinically thyrotoxic. In 1 case a biopsy of the thyroid was taken before thiouracil was begun. Comparison of the histologic appearance of this tissue with that removed at operation (Fig. 2) shows the persistence of the typical thyrotoxic changes.

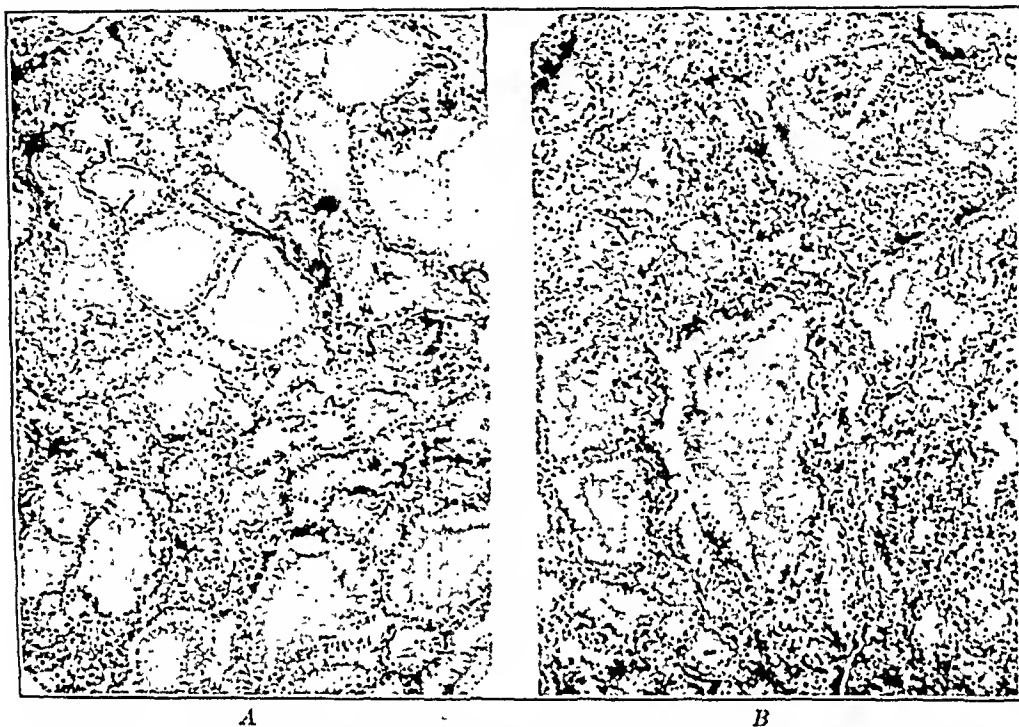


Fig. 2.—Histologic appearance of toxic thyroid of patient V. McC. A, Before treatment (biopsy); B, after 23 days on thiouracil (thyroidectomy).

Three patients who had received thiouracil were subsequently operated upon following iodization, at intervals of 5, 6 and 7½ weeks after the withdrawal of thiouracil. Two of these patients failed to show a marked preoperative response to iodine, although their postoperative courses were not unusual. Sections from the thyroids of 2 of these patients showed some evidence of involution, although the colloid was somewhat thinner than usual and showed peripheral vacuolization. The thyroid of the third patient, which was markedly and diffusely enlarged, showed advanced involution with large amounts of colloid, despite the fact that he was severely toxic and resistant to both thiouracil and iodine.

Complications of Treatment. Untoward reactions attributed to thiouracil were observed in 8 patients.* The most important complication was that of severe leukopenia, associated with pharyngitis and fever, which was observed in 2 cases. The first patient was a white woman aged 41 years. Her leukocyte count dropped to 1200 per

* One of these patients who exhibited urticaria has not been included in our series because the diagnosis of thyrotoxicosis was doubtful.

c.mm. (28% neutrophils) after receiving thiouracil for 23 days. Two days later the leukocyte count was 1850 per c.mm. (12% neutrophils), her temperature had risen to 104° F. and there was severe acute tonsillitis and pharyngitis. No localized ulcerative or necrotic lesions appeared in the mouth or pharynx. Thiouracil was stopped when the leukopenia was first noted, and pentose nucleotide injections were started when the fever appeared. The pharyngitis and fever subsided in 3 days and the leukocyte count returned to 3800 per c.mm. (30% neutrophils) on the 5th day. Eight days later thiouracil was again given in doses of 0.2 gm. daily, but after 6 days the leukocyte count again fell to 2400 per c.mm. and the drug was again stopped, although other symptoms did not reappear. After an interval of 1 month thiouracil was again started cautiously in doses of 0.2 gm. daily, and no subsequent fall in leukocyte count occurred, although treatment was continued for 2 months. The thyrotoxic phenomena then subsided and the patient has remained well for 3 months without medication.

The second patient was a white man, aged 22 years. After receiving thiouracil in doses of 0.6 to 1 gm. daily for 9 days, pharyngitis, chills and fever appeared with a leukocyte count of 2200 per c.mm. (69% neutrophils). The drug was stopped and her signs and symptoms disappeared within 3 days. After 33 days thiouracil was resumed. After taking 0.4 gm. in divided doses, fever (100.4° F.), cervical adenitis and slight pharyngitis appeared, although the leukocyte count remained normal. This patient gave a history of allergy, and had developed a dermatosis following iodine therapy 6 years previously.

In addition, 14 other patients whose leukocyte counts were within normal limits prior to the institution of thiouracil therapy, showed a fall in total leukocyte count below 5000 per c.mm. within 4 to 55 days after the drug was begun. In 6 of these patients, the leukocyte count returned to normal levels despite continuation of therapy. One patient whose count fell from 8200 to 4100 per c.mm. after 10 days on thiouracil, showed a normal leukocyte count on the following day. Normal leukocyte levels were maintained thereafter while the daily dosage of thiouracil remained at 1 gm. for 7 months. At the end of that time the leukocyte count had again fallen to 2800 per c.mm. with a normal differential formula. Splenomegaly and moderate generalized adenopathy were found before treatment was begun; the splenomegaly later disappeared. Aspirated sternal bone marrow examined at the time leukopenia first appeared was normal.

Two patients developed mild maculopapular facial eruptions 11 and 19 days respectively after beginning treatment. Two patients, both of whom gave histories strongly suggestive of allergy, complained of urticaria after 7 and 8 days respectively on the drug.* One of these patients showed slight edema of the ankles and a plasma chloride concentration of 106 milliequivalents per liter after taking thiouracil for 1 month. Mild pharyngitis and fever, probably attributable to

* One of these patients who exhibited urticaria has not been included in our series because the diagnosis of thyrotoxicosis was doubtful.

thiouracil, appeared in 1 patient after 10 days of treatment. One patient complained of myalgia and anorexia 48 hours after the institution of treatment, and showed a regular evening rise in temperature to 101° F. which continued until thiouracil was stopped after 2 weeks. Despite these reactions, her basal metabolic rate fell to normal, and auricular fibrillation, which had previously been present, disappeared. One patient, who had previously taken the drug for 43 days without untoward effect, developed severe pruritus 21 days after resumption of thiouracil.

Comment on Selected Cases. Examination of the patients who failed to respond satisfactorily to thiouracil does not show any significant common factor or pattern. The following patients showed only a partial response to treatment.

Case Reports. **CASE 1.** J. B., an unmarried white girl, age 19, had thyrotoxic symptoms for about 3 months. Nervousness and tachycardia were prominent. There was moderate exophthalmos, but the thyroid gland was only slightly enlarged. The basal metabolic rate was +62%. The patient was kept at rest in the hospital for 17 days and thiouracil was given in daily doses of 0.6 to 1 gm. for 27 days. The basal metabolic rate fell to +24% after 14 days of treatment, but had risen again to +41% after 27 days of treatment. During this time the serum cholesterol rose from 179 to 291 mg. per 100 cc. Subjective improvement was slight, and she gained only 3 pounds. Thiouracil was withdrawn after 27 days and thyroid irradiation was begun. A marked aggravation of symptoms followed the institution of irradiation and this treatment was stopped after 1 week. Twenty-six days later, pre-operative iodization was begun. After 13 days of iodine therapy her basal metabolic rate was still +38%. Subtotal thyroidectomy was performed at this time. Three months after operation she had gained 20 pounds but still showed a moderate tachycardia and her blood pressure was 140/100. Her menses had stopped and growth of hair on the lower abdomen was noted. The hypertension, amenorrhea and beginning hirsutism suggest the possibility that her thyrotoxicosis may have been an early episode in the development of Cushing's disease.

CASE 2. A. B., a white male, age 47, was first seen 2 months after the explosive onset of severe hyperthyroidism with very slight enlargement of the thyroid gland. The basal metabolic rate was +48%, there was severe ophthalmopathy with edema of the lids and conjunctiva, superficial corneal erosion, occasional diplopia and an exophthalmometer reading of 28 mm. in each eye. In addition to thiouracil the patient was kept at bed rest in the hospital, receiving a high caloric diet with extra vitamins, sedation and estrogenic substance by mouth. He also received a total of 2000 r units of irradiation to the pituitary area. There was gradual but steady improvement; after 43 days on thiouracil his basal metabolic rate had fallen to +7%, the heart rate was 76 and he had gained 7 pounds. All the ocular phenomena except the exophthalmos gradually disappeared. He remained well with steadily increasing weight for 3½ months, at the end of which time he was allowed to return to work. Two weeks later his basal metabolic rate had risen to +28% and tachycardia, palpitation and nervousness recurred. Thiouracil was resumed in dosage up to 2 gm. daily, but after 3 weeks of such therapy his basal metabolic rate was +30% and his pulse rate was 132 per minute. The exophthalmos persisted, but the other ocular phenomena did not recur. At this time severe generalized pruritus appeared and thiouracil was stopped. Thyroidectomy has been avoided because of the severe ophthalmopathy. The patient has subsequently received intermittent iodization alternating with thyroid irradiation. At the time of writing he is still moderately thyrotoxic with a basal metabolic rate of +19%.

CASE 3. R. S., a white married woman, age 35, when first seen was about 4 months pregnant. Enlargement of the thyroid had been noted since the age of 9, but had increased markedly during her pregnancy. Although she denied symptoms, there was evidence of definite thyrotoxicosis. The thyroid gland was markedly and diffusely enlarged and the basal metabolic rate was +27%. Her resting pulse rate was 110 per minute. There was a presystolic apical murmur and the cardiac contour in the orthodiagram suggested mitral stenosis. The patient was kept at bed rest in the hospital for 15 days, during which time thiouracil was given in doses of 0.8 to 1 gm. daily. After 29 days her basal metabolic rate had fallen to -1 per cent and thiouracil was withdrawn. One month later the basal metabolic rate had again risen to +27% and thiouracil was again begun in dosage of 0.4 gm. daily. At this time the administration of iodine (10 mg. daily) was also instituted in order to insure an adequate supply of iodine for the fetus. Although thiouracil was continued in daily doses of from 0.4 to 0.8 gm. for the next 8 weeks, the patient's basal metabolic rate varied from +32 to +45%, the thyroid increased further in size and intermittent tachycardia persisted. Thiouracil was stopped 1 week before delivery and Lugol's solution was given in daily doses of 2 cc. The patient was delivered at term, without difficulty, of a healthy male infant which showed no evidence of thyroid enlargement or dysfunction. Seven weeks after delivery and 8 weeks after withdrawal of thiouracil her basal metabolic rate was +37%, the thyroid enlargement had increased further and the patient still appeared markedly thyrotoxic. Thyroidectomy was advised but not accepted. It is quite possible that this patient's pregnancy may have prevented a more complete response to thiouracil.

CASE 4. W. B., a white male, age 68, had been nervous, with tachycardia and intermittent abdominal pain, for 7 months, during which time he had lost 60 pounds. A diagnosis of gastric ulcer was made in another hospital after two periods of treatment and study, including Roentgen ray examination. Two months before admission he had received iodine for a period of 2 weeks. Examination showed marked weight loss and tachycardia with a tremendous increase in cardiac output (+234%). The thyroid was only slightly enlarged. The basal metabolic rate was +72%. There was no Roentgen evidence of peptic ulcer. The basal metabolic rate fell to +30% after the patient had received 1 gm. thiouracil daily for 2 weeks. After 1 month of such treatment, during which time he was hospitalized and given a high calorie diet with supplementary vitamins and sedatives, his basal metabolic rate was still +31% and his tachycardia had not materially decreased. However, he had gained 11 pounds, was subjectively much improved and his cardiac output had fallen to +128%.

The following 2 cases failed completely to respond.

CASE 5. W. L., a white male, age 29, had had thyrotoxic symptoms for 10 months prior to admission, with loss of 50 pounds. He had received large doses of iodine for 2½ months before we saw him. On admission to the hospital he presented a classical picture of extremely severe thyrotoxicosis, showing marked weight loss, sweating, tremor, muscular weakness, exophthalmos and a very large diffuse firm goiter. The basal metabolic rate was +75%. He received thiouracil in daily dosage of 0.6 to 0.8 gm. for 23 days without evidence of sustained improvement. The basal metabolic rate fell to +48% on the 14th day of treatment, but on the 23rd day had again risen to +73%. During this time he lost 7 pounds, and his tachycardia did not subside. After the withdrawal of thiouracil he was again given iodine, and a right hemithyroidectomy was successfully performed 16 days later. Two months later a left hemithyroidectomy was performed after another period of iodine therapy, with eventual complete relief of the thyrotoxicosis. This patient was the first in our series to receive thiouracil (June, 1943) and we did not at the time appreciate the effect of previous iodization upon the response of the toxic thyroid to thiouracil. It is possible that a more prolonged period of therapy with the latter drug might have produced more satisfactory results.

CASE 6. M. H., a white female, age 26, had had symptoms of thyrotoxicosis for about 8 months. She had received iodine for two periods of 8 and 3 weeks respectively during the 7 months prior to admission to the hospital. There was slight diffuse thyroid enlargement and moderate exophthalmos, and her initial basal metabolic rate was $+33\%$. She also presented definite evidence of myasthenia gravis, which was confirmed by her response to prostigmine. She received thiouracil in daily dosage of 0.6 to 1 gm. for 40 days without favorable subjective or objective response. During this period she lost 3 pounds. Her basal metabolic rate rose to $+44\%$ after 12 days of treatment, fell to $+14\%$ on the 32nd day and rose again to $+22\%$ on the 40th day. On the 2nd day of treatment she developed a diffuse respiratory infection with fever up to 102° F. and received sulfadiazine for 2 days. Irradiation therapy to the thyroid and thymus areas was begun 25 days after the withdrawal of thiouracil. The thyrotoxic manifestations have almost completely disappeared after two series of irradiation and there has been concomitant improvement in her myasthenia, although she still requires prostigmine and ephedrine. This patient has been consistently unable to cooperate satisfactorily in her basal metabolism determinations and all of the values obtained are open to question. There can be no doubt, however, as to the existence of both the thyrotoxicosis and myasthenia gravis. Her improvement following irradiation therapy is likewise beyond question.

The following cases are described briefly because of some features of unusual interest.

CASE 7. A. S., a colored male, age 48, had had thyrotoxic symptoms for 16 months, with a 30 pound weight loss. Examination showed exophthalmos with stare, emaciation, muscular weakness with marked tremor, diffuse nodular goiter of moderate degree, auricular fibrillation, generalized adenopathy and slight enlargement of the spleen. The basal metabolic rate was $+62\%$; there was a slight lymphocytosis (leukoocytes 8200 per c.mm. with 54% lymphocytes). After 22 days on thiouracil, during which time he also received digitalis, a high caloric diet and extra vitamin B with continuous bed rest in the hospital, he showed little evidence of improvement. Auricular fibrillation was still present, he had lost 2 pounds, and his basal metabolic rate was $+31\%$. Subtotal thyroidectomy was advised, but was refused. The patient requested that he be allowed to continue thiouracil while resuming his work as a cement finisher, and this request was somewhat reluctantly granted. Two weeks after discharge from the hospital, on a daily dose of 0.6 gm. of thiouracil, his basal metabolic rate was $+55\%$ and auricular fibrillation persisted, but he had gained 14 pounds with no evidence of congestive heart failure and felt much better. Six weeks later his basal metabolic rate was $+26\%$, he had gained another 7 pounds, the cardiac rate was 90 per minute and the rhythm was regular. The spleen was still palpable but the adenopathy was less marked. The daily dose of thiouracil was increased from 0.6 to 0.8 gm. Except for one 10-day period the patient took thiouracil for 6 months continuously after leaving the hospital. At the end of that time he had gained 28 pounds, the cardiac rate and rhythm were normal, splenomegaly had disappeared, the goiter was somewhat smaller and his basal metabolic rate was $+5\%$. His eyes, however, had increased 1 mm. in prominence and the leukocyte count had fallen to 2800 per c.mm. with a normal differential formula. Thiouracil was then stopped because of the leukopenia and the disappearance of the thyrotoxic phenomena. This case illustrates the occasional necessity for prolonged therapy with thiouracil before satisfactory response is obtained, as well as the fact that leukopenia may appear or reappear after the prolonged administration of thiouracil.

CASE 8. E. M., a white female, age 50, had had several attacks of rheumatic fever in childhood, and heart disease had been diagnosed at the age of 20. She had been under medical treatment for recurrent congestive heart failure for 2 years prior to admission. Following the death of her husband

9 months before admission, she had become increasingly weak and dyspneic and had lost about 40 pounds. Examination showed marked nervousness, tremor, slight stare, auricular fibrillation, signs of congestive heart failure, and evidence of mitral stenosis and regurgitation with probable tricuspid regurgitation. There was no thyroid enlargement. The basal metabolic rate was +47%. Her response to digitalis and other measures directed toward relieving the circulatory failure was unsatisfactory, and the ventricular rate remained rapid. She likewise failed to improve after the administration of potassium iodide for 1 month. At this time, when her basal metabolic rate was +34%, the potassium iodide was replaced by thiouracil in dosage of 1 gm. daily. After 12 days the basal metabolic rate was +15% and the congestive phenomena had markedly improved; although she continued in auricular fibrillation the ventricular rate had fallen to approximately 90 per minute. She continued her medication at home for 2 weeks after which she returned to the hospital. At this time, after 6 weeks of thiouracil therapy, her basal metabolic rate was +11% and remained at that level until her discharge 2 weeks later. During this time she received Cedilanid (2 mg. daily) and 2 cc. of a mercurial diuretic by intravenous injection 3 times weekly. She remained in auricular fibrillation, but the ventricular rate remained between 80 and 90 per minute and she presented no evidence of congestive heart failure except a firm enlargement of the liver (cardiac cirrhosis). There was marked improvement in her nervousness. Thyroidectomy was advised but not accepted.

The diagnosis of thyrotoxicosis could not be made with certainty in this case, as the initial high basal metabolic rate might have resulted from her congestive heart failure. However, thyrotoxicosis was strongly suggested by the history of weight loss, the stare, nervousness and refractoriness to digitalis. Her marked improvement and the concomitant decline in basal metabolism following thiouracil likewise suggest a thyrotoxic factor. If it be assumed that thyrotoxicosis was not present, her apparent response to thiouracil still remains of interest, since in this event it would suggest that some antithyroid action of the drug upon a normally functioning gland may have been a factor contributing to her recovery from congestive heart failure (see Comment).

CASE 9.—V. McC., a white male, age 27, had first had thyrotoxic symptoms at the age of 24. A partial thyroidectomy was performed soon afterwards in another hospital which he left, against advice, 3 days after operation. His symptoms persisted with progressive weight loss of 74 pounds until his admission to our hospital 3 years later. At that time he was severely emaciated with marked muscular weakness and tremor, exophthalmos and a nodular goiter. The basal metabolic rate was +38%. He had taken iodine for 3 weeks prior to admission. A preoperative biopsy of the thyroid was taken, but the patient left the hospital against advice before thiouracil could be started. He was readmitted 11 days later, having taken iodine for several days during the interval. After taking thiouracil in doses of 1 gm. daily for 16 days, his basal metabolism was +28%, but he had gained 15 pounds, his pulse rate had declined, and he was anxious for operation. His preoperative course was marked by several episodes of morning vomiting which were inexplicable at the time but which in the light of later knowledge seemed due to alcoholism. After 16 days of thiouracil therapy, a subtotal thyroidectomy was performed. The patient took the anesthesia badly, became cyanotic and went into shock on the table after losing a rather large amount of blood. The thyroid gland was much larger than it had seemed on palpation. It was extremely vascular and friable. Bleeding was very free and difficult to control. Despite several transfusions of blood and plasma, the patient remained in serious condition and did not react from the anesthesia. He died 20 hours after operation, presenting the picture of combined shock, anoxia and thyrotoxic crisis.

Necropsy showed bilateral bronchopneumonia with a histologic appearance which suggested that it had been present for about 3 days. Sections of the thyroid (see Fig. 2) presented an appearance quite unlike that of the iodized

toxic thyroid or the untreated toxic gland and resembled that described by Williams and Chute¹¹ in the toxic thyroids of patients treated with thiouracil. There was hypertrophy and hyperplasia of the epithelial acinar cells with marked reduction in colloid content of the acini and there was an increase in the vascularity of the gland with marked congestion. The pituitary, parathyroids and testes were normal. There was congestion in the spleen and kidneys and the liver showed slight fatty dystrophy.

It seems unlikely that thiouracil was a factor in this unfortunate fatality. In retrospect, it is obvious that we should not have permitted the patient to undergo thyroidectomy and that the operation, once begun, should have been discontinued when he reacted badly to the anesthetic. The pathologic report of a 3 day old bronchopneumonia is difficult to understand as the patient presented neither fever, leukocytosis, nor any sign or symptom suggesting such a process. It was later discovered that the patient had been in the habit of consuming much more alcohol than was realized at the time of his admission.

CASE 10.—V. M., a 13 year old girl, developed symptoms of thyrotoxicosis about 1 month before admission to the hospital. She had suffered several attacks of rheumatic fever beginning at the age of 6. Between the ages of 7 and 11 she had several epileptiform seizures. Glycosuria was discovered at the age of 12 and she had received 20 units of protamine zinc insulin and 10 units of unmodified insulin daily since that time. Examination showed slight exophthalmos, a moderate, diffuse thyroid enlargement, tachycardia, tremor, and a loud apical systolic murmur. The basal metabolic rate was +27% and the fasting blood sugar was 102 mg. per 100 cc. After receiving thiouracil in daily doses of 0.6 to 1 gm. for 10 days, her basal metabolic rate had fallen to +3% and her thyrotoxic symptoms were well controlled. Her thyrotoxicosis remained under satisfactory control on daily doses of thiouracil varying from 0.2 to 1 gm. for 5½ months. During this time she gained 31 pounds, but her insulin requirement increased. After 5½ months of treatment with thiouracil she required 30 units of protamine and 25 units of unmodified insulin in the morning and 25 units of unmodified insulin in the evening to prevent glycosuria on a diet containing 120 gm. of protein, 120 gm. of fat and 260 gm. of carbohydrate. Her fasting blood sugar at that time was 122 mg. per 100 cc.

Several possible factors may have operated in the case to prevent the amelioration of the diabetes which might have been expected to accompany the improvement in the thyrotoxicosis. Such factors might include progressive growth, the onset of menstruation which occurred while she was under treatment, and possibly the production of increased diabetogenic activity in the anterior pituitary by thiouracil. Failure of the diabetes to improve concomitantly with the control of the thyrotoxicosis is in contrast to the usual amelioration of diabetes when associated thyrotoxicosis is controlled by irradiation or thyroidectomy.

Comment. Our experience with thiouracil in the prolonged treatment of thyrotoxicosis agrees in general with that reported by other observers. We have likewise encountered the same types of complications and toxic effects as have been reported elsewhere. Among these, neutropenia with associated pharyngitis and fever appears to be the only one of major importance. The failure of exophthalmos to recede in our cases, and its occasional aggravation following thiouracil, do not confirm some other observations. (See footnote, p. 562.) Thyrotoxic patients do not seem to become refractory to thiouracil, and those who relapse when the drug is withdrawn can apparently be brought under control repeatedly by its readministration. The ability of most patients to remain ambulatory, or even to continue at work,

while under treatment for long periods of time constitutes an important advantage. Bed rest at initiation of treatment shortened the time of response. Examination of our patients who failed to respond satisfactorily shows no apparent common factor. However, such factors as pregnancy, myasthenia gravis, prolonged iodization prior to treatment and a possible background of a larval Cushing's disease existed in 4 cases. In Case 5 it is possible that a more prolonged period of treatment with thiouracil might have produced a better response. In Case 3 the patient's refractoriness to the resumption of thiouracil may have been due to an underlying hyperfunction or dysfunction of the anterior pituitary.

A number of important questions remain to be answered regarding the effect and clinical usefulness of thiouracil. Among these are:

1. What late toxic effects may follow its prolonged use? Is it possible, for example, that depression or exhaustion of the bone marrow might follow the prolonged ingestion of the drug in some cases?

2. What undesirable dislocations of endocrine relationship might be induced by prolonged inhibition of thyroid hormone production and the consequent disturbance of thyroid-pituitary balance? Is there thus a possibility that hyperfunction of the pituitary might eventually be produced, or that pituitary exhaustion might ensue? Is it possible that the maintenance of a chronically hyperplastic state of the thyroid might be followed by fibrosis, or atrophy, or neoplastic change?

3. What is the effect of thiouracil upon the structure and function of the normal human thyroid? Observations reported to date on such an effect are inadequate. Much further work appears desirable in an effort to explain the discrepancy between the consistent effects of thiouracil in normal lower animals and its apparent lack of effect on the normal human. Our observations in Case 8 suggest the possibility that there may be some action upon the normal human thyroid which might prove of considerable therapeutic value in congestive heart failure and certain other disorders.

4. What types of thyrotoxicosis will respond best to thiouracil, and how long must such cases remain under treatment before a permanent cure is effected?

5. Could the therapeutic response in thyrotoxicosis be enhanced by the coincidental use of antipituitary agents such as irradiation, estrogens or androgens?

The observation of many more cases over a much longer period of time will be necessary before these questions can be answered, and before the usefulness of thiouracil can be ultimately evaluated. Evidence available at present would appear to justify the tentative conclusion that thiouracil may be useful: (a) in the preoperative preparation of patients with severe or complicated thyrotoxicosis, and (b) in the prolonged treatment of patients with mild or moderate uncomplicated thyrotoxicosis.

The failure of some of our patients to respond to thiouracil raises again the possibility that certain types of thyrotoxicosis may be the

result of dysthyroidism rather than hyperthyroidism. This concept was suggested by Plummer⁷ in an effort to explain what he believed to be the unresponsiveness of patients with toxic nodular goiter to iodine. The theory of dysthyroidism (that is, a toxic state resulting from the production of an abnormal hormonal product of the thyroid gland rather than an excess of a normal hormonal product) has received little attention in recent years. It is, however, supported to some extent by the following evidence: (a) Complete and lasting reproduction of the thyrotoxic syndrome as it exists in man cannot be achieved experimentally either by thyroxinization or by the administration of anterior pituitary hormones. (b) A number of clinical and experimental observations suggest that certain types of goiter may exert a specific cardiotoxic influence without producing a typical thyrotoxic syndrome.

It is conceivable that the failure of certain thyrotoxic patients to respond to thiouracil might be due to the fact that their toxicity is due to an abnormal thyroid hormone, and that the production of such an abnormal hormone cannot be interrupted by thiouracil.

Although toxic goiters do not usually become smaller during the first few weeks of thiouracil therapy, Williams and Clute¹¹ have reported definite reduction in size of the goiters in several of their cases after prolonged treatment. We have likewise observed this reduction in size in 8 of our patients after periods of treatment varying from 2½ to 9 months. It has been suggested⁸ that such late reduction in size might be the result of exhaustion atrophy or fibrosis. However, it also seems possible that exhaustion of thyrotropic hormone production by the anterior pituitary might be a factor. This possibility could be investigated by measurement of the urinary excretion of thyrotropic-pituitary hormone in patients showing such reduction in size of the thyroid.

Summary and Conclusions. Clinical experiences with 37 cases of thyrotoxicosis treated with thiouracil have been described. Thirty patients (81%) showed a favorable response, 4 (10.9%) showed a partial response and 2 (5.4%) showed no response to treatment. Three of the 6 patients showing unsatisfactory response presented associated conditions which may have influenced their reactions.

In 4 patients thiouracil was used during preparation for thyroidectomy. One of these died 20 hours after operation, but thiouracil was not regarded as a factor in his death. Necropsy in this case showed no lesions which could be associated with the use of thiouracil.

The control of thyrotoxicosis with thiouracil in a 13 year old girl with diabetes mellitus was not followed by an increase in her carbohydrate tolerance or a decrease in insulin requirement.

The histologic appearance of the thyroid gland in our patients prepared for thyroidectomy with thiouracil showed the hyperplasia and other changes previously reported by others.

Eight patients have remained in remission for periods varying from 3 weeks to 7 months following the complete withdrawal of thiouracil;

on minimal doses (0.1 to 0.2 gm. daily) 3 patients have responded likewise. Thirteen patients relapsed when the drug was either reduced in dosage or withdrawn; all of these patients, however, again responded to readministration of thiouracil.

Measurements of cardiac output by ballistocardiogram in 9 patients showed a general tendency toward reduction in output under thiouracil therapy which was roughly parallel with the decline in basal metabolism.

No evidence of development of refractoriness to thiouracil was observed.

Untoward reactions attributable to the drug occurred in 8 patients. The most important of these was neutropenia with pharyngitis and fever, noted in 2 cases. Reduction in the size of the thyroid gland was noted in 8 patients after prolonged treatment. Exophthalmos tended either to remain stationary or to increase slightly.

While much further work remains to be done before the clinical usefulness of thiouracil can be finally evaluated, it may tentatively be concluded that this drug effectively controls most of the phenomena of thyrotoxicosis in the large majority of patients, and that its use at present is justified in the protracted treatment of mild or moderately severe cases and in the preoperative preparation of selected patients for thyroidectomy. It may also prove of considerable value in patients regarded as unacceptable surgical risks.

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THE USE OF PENICILLIN IN TOPICAL APPLICATION

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With the Technical Assistance of
VALENTINE J. CONNOLLY, B.S.

OWING to the shortage of penicillin, a technique for the extraction of penicillin from the urine of patients under treatment for syphilis, gonorrhea and septic infections was developed by the author.¹ It was found practical and inexpensive, yielding 30 to 40% of the antibiotic substance administered. A considerable number of animal and clinical trials demonstrated that the reclaimed penicillin was non-toxic and non-pyrogenic when used parenterally. Dosages as high as 2,000,000 units a week were administered intramuscularly with excellent clinical results, differing in no way from therapy with commercial penicillin. We have decided therefore that the reclamation of penicillin is a useful means of economizing the substance under conditions of scarcity. No noteworthy information concerning the effectiveness of penicillin therapy in infections can be added from this experience to the data presented by Keefer and his co-authors.² However, the availability of the material has encouraged us to make certain observations concerning the use and desirability of topical applications.

It has been observed that penicillin administered intramuscularly or intravenously rapidly permeates the body fluids, excepting the spinal fluid, saliva and tears.³ Clinical observation made us believe that the nasal accessory sinuses and the skin may frequently be inadequately treated even with high dosages given by the intramuscular route. Two cases illustrate this point.

Case Reports. CASE 1. P. T., a 20 year old male with chronic rheumatic endocarditis, was under treatment for *Streptococcus viridans* septicemia, receiving 300,000 to 500,000 units of penicillin daily for 25 days. This case will be reported in a separate paper. The bacteremia was controlled and the constitutional improvement was excellent, but the patient had considerable nasal discharge from which *Strep. viridans* was cultured. The frontal and maxillary sinuses appeared abnormally opaque in roentgenograms. A saline dilution of penicillin, 1000 units per cc., was sprayed into the nose at frequent intervals with a nasal atomizer. In this way about 20,000 units of penicillin were administered daily. Penicillin was excreted in small amounts in the urine during this therapy. The clinical effect was good and nasal discharge became scanty after 5 days.

CASE 2. W. K., a 70 year old male, was treated with 200,000 units of penicillin by intramuscular injection daily for 30 days, in a clinical trial to determine the effect of the antibiotic on his disease, squamous carcinoma of the skin. At the end of this period, staphylococci were readily detected in biopsy sections in crypts of the tumor. Penicillin was subsequently administered by topical application with electrophoresis and the organisms were not to be found after the first day of treatment. The patient's thumb was being exposed to a solution of 5000 units per cc. with a 5 ma. current passed through it. A 30 minute treatment resulted in absorption of penicillin, as demonstrated by the excretion of about 1 unit per cc. of urine during the subsequent 4 hour period.

Observations concerning the employment of penicillin in the control of gingivitis and Vincent's infection of the mouth are being made and will shortly be published by Strock.⁴ The clinical effectiveness of 5000 units of penicillin applied as a mouth irrigant once a day is as great as that of large intramuscular doses. The absence of penicillin in the saliva after parenteral administration was noted by Rammelkamp.³

The use of an ointment for maintaining a local supply of penicillin on the skin was suggested by Clark, Colebrook, Gibson and Thompson,⁵ Florey and Florey,⁶ and Bodenham.⁷ Since doubt was felt concerning the release of penicillin from an ointment base, the following *in vitro* tests were performed:

Two ointments were prepared, one with lanolin as a base and the other using a vanishing cream base, each containing 1000 units of penicillin per gm. One batch in vanishing cream base had Aerosol MA added in amounts of 0.1 and 1%. Other penetrating and wetting agents (Triton and Duponol C) were also tried. Since none of these mixtures exceeded the effectiveness of 0.1% Aerosol MA, subsequent experiments were standardized on this. A 1.5% agar medium was inoculated heavily with *B. subtilis*, and after thorough agitation was transferred to tubes. After cooling and solidification, the surface of each tube was covered with a thin layer of one of several materials under test, and the depth of inhibition was measured from the line of contact to the layer of bacterial growth (Fig. 1). The results follow:

Tube	Contents	Bacterial inhibition
1	Ointment base with Aerosol 0.1%	None
2	Lanolin with 1000 units penicillin per gm.	6.0 mm.
3	Penicillin solution, 1000 units per cc.	16.5 mm.
4	Ointment with Aerosol and 1000 units per gm.	15.0 mm.
5	Above ointment without Aerosol (not illustrated)	13.0 mm.

The conclusion reached from these observations which were repeated several times was that in a suitable ointment base penicillin when applied topically has a considerable ability to penetrate a solid agar culture medium, and penetration is enhanced by the addition of a wetting agent (Aerosol).

A second experiment was designed to demonstrate any penetration of penicillin applied as an ointment through tissue. The technique was as follows:

Technique. Short lengths (5 to 7 cm.) of wide glass tubing (12 mm.) were covered over one end by pieces of fresh skin obtained at circumcision operations. The cutaneous surface was toward the tube lumen, and the tubes were partially filled with the material under test. Each tube was then placed firmly over an agar culture seeded with *B. subtilis* in a test tube wide enough to admit the skin-covered tubing. There was no evidence of inhibition of bacterial growth through the skin layer whether by aqueous dilutions of penicillin up to 1000 units per cc., or by ointments containing a similar concentration of penicillin, both with and without wetting agents.

As a check on the failure of these *in vitro* attempts to demonstrate penetration, 25,000 units of penicillin were applied as an injection in

ointment with Aerosol. Urine was collected for the 4 hour period following inoculation and failed to demonstrate any penicillin content within the range of our test (0.3 unit per cc.). Further attempts with higher penicillin dosages are being made, but it is apparent that diffusion through the skin is certainly too small for therapeutic utility.

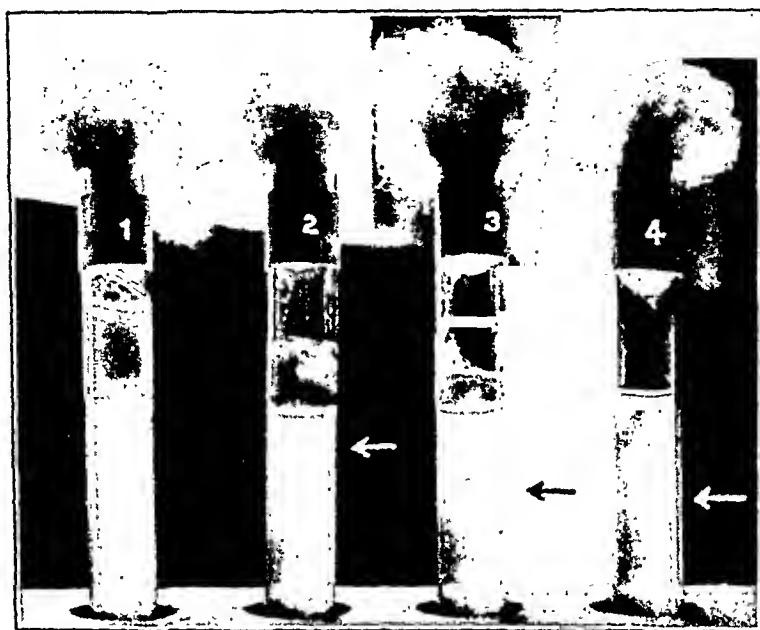


FIG. 1.—Penetration of penicillin through agar from 3 media. The tubes contain: 1, vanishing cream ointment with Aerosol 0.1%; 2, lanolin containing 1000 units penicillin per gm.; 3, ointment with Aerosol containing 1000 units penicillin per gm.; 4, aqueous dilution of penicillin, 1000 units per cc. The penetrating ability of penicillin is almost as great in the ointment base with Aerosol as in aqueous solution.

Clinical use of the penicillin Aerosol vanishing cream ointment has been made in a number of types of cases, as follows:

Diagnosis	Duration	Results
1. Syecosis barbæ	3 wks.	Excellent in 2 days
2. Syecosis barbæ	5 wks.	Excellent in 4 days
3. Furunculosis	6 days	Good
4. Furunculosis	4 days	Good
5. Furunculosis	11 days	Good
6. Furunculosis	3 days	Good
7. Furunculosis	3 days	Good
8. Chronic cellulitis; ulceration (postop. osteomyelitis)	9 mos.	Good
9. Chronic cellulitis; ulceration (postop. osteomyelitis)	7 mos.	Good
10. Indolent ulcer (sybiotic infection)	4 mos.	Improving (2 wks.)
11. Chaneroid	1 wk.	Excellent in 7 days

The appearance of a zone of infection under treatment by the ointment is characterized by hyperemia and arrest of suppuration. In an uncomplicated situation, like a furuncle, the first change is seen after 24 hours in a lessening of the peripheral edema and reduction in tension of the lesion. Early furuncles resolve in 4 to 6 days, but suppurating ones will go on to evacuation. Chronic pyogenic infections

respond slowly and develop a considerable zone of hyperemia when the ointment is applied for extended periods. The granulation tissue growth is accelerated and the surface becomes engorged. Similar observations have been made by Bodenham.⁷

Discussion. In his review of his discovery of penicillin, Fleming⁸ makes the comment that "perhaps the most important use of penicillin is locally in more or less minor infections and not in the dramatic cases in which patients are snatched back from death." The observations made here tend to emphasize the use of topical penicillin application. When consideration is given to the difficulty and expense of maintaining over a period of many days or weeks a high penicillin concentration by parenteral administration, topical applications, when practicable, offer a suitable alternative. It is possible to reach local levels of penicillin activity by topical administration far in excess of the highest ranges we have maintained by intravenous and intramuscular use, namely 0.7 to 0.9 units per cc. of blood achieved by continuous introduction at the rate of 20,000 units per hour. There are many bacteria, including some strains of staphylococci, which are resistant to low penicillin concentrations, or even to the high levels noted above, but are susceptible at still higher levels. For the control of such infections, penicillin may be applied topically or by both parenteral and topical routes. Pereyra and Landy⁹ noted the failure of ordinary doses of penicillin administered intramuscularly to affect chancroid. On the other hand, local application of penicillin ointment has been more rapidly curative than treatment with sulfonamides.¹⁰

Summary. 1. Evidence is cited indicating that penicillin administered parenterally may not reach a sufficient concentration in certain regions for therapeutic effectiveness. Topical application in such regions has, in several instances, been successful.

2. Penicillin incorporated in a suitable ointment, together with a wetting agent, penetrates agar sufficiently to cause inhibition of *B. subtilis* at a depth of 16 mm. Although it does not demonstrably penetrate through a skin layer *in vitro*, penicillin in such an ointment base has, in our experience, strikingly effective value in acute and chronic pyogenic infections of the skin and subcutaneous tissues, particularly in syccosis barbæ, infected superficial wounds and furunculosis.

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PENICILLIN
WITH SPECIAL REFERENCE TO ITS USE IN INFECTIONS
COMPLICATING DIABETES*

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THE efficacy of penicillin in treatment of certain types of pyogenic infections, together with its remarkable lack of toxicity, suggested that the drug might be particularly useful in the management of some of the more localized and generalized coccic infections so frequently encountered in association with diabetes mellitus. Chemotherapy with sulfonamides, as pointed out by Styron, Brondley and Root,¹² while of undoubted value in controlling the extension of infections, cannot be expected to cure necrotic lesions such as carbuncles and gangrene. The experience here described began when penicillin was still a laboratory curiosity, and because supplies were so limited and impure, the early cases were treated by infiltration of the drug, and the patients did not receive what are now believed to be adequate doses. Nevertheless, the responses obtained by local infiltration of penicillin directly into infected areas, when compared with general administration have been so striking that it seems worthwhile to direct further attention toward this method of administration.

In 1929 Fleming² made his observation that around a large colony of *Penicillium notatum* which accidentally contaminated one of his culture plates of staphylococcus, the colonies became transparent. Instead of discarding the contaminated plate, Fleming's curiosity was aroused and he endeavored to find out what it was in *Penicillium* that brought about this antibacterial action. Subsequent experiments showed that the active substance was soluble and filterable and that it had activity against staphylococci, hemolytic streptococci, pneumococci, gonococci and *Bacillus diphtheriae*, but not against *B. coli* or *B. influenzae*. During the next decade the sulfa drugs were developed and it was not until 1940 that Florey and his group³ at Oxford discussed penicillin, as the active substance had been termed, as a chemotherapeutic agent.

By 1941, 10 clinical cases unresponsive to the usual chemotherapeutic agents had been accumulated,¹ and great interest had been aroused in the new antibiotic agent. Thus, discovery of penicillin and its recent intensive development for therapeutic use were both due to British scientists, Fleming and Florey and their collaborators at Oxford.

The research leading up to the large-scale production of penicillin may well be claimed as an instance of collaboration without parallel in the history of the pharmaceutical industry. Collaboration has been

* Presented April 11, 1944, before the Medical Society of the County of Oneida, Utica, New York.

freely carried out between scientific workers in both industrial and academic fields. There has been complete mobilization of all the skill and knowledge in both Britain and the United States for speeding the solution of problems of manufacture of this most unusual drug, as well as complete coöperation in solving the clinical problems presented in determining how penicillin may best be applied in the actual treatment of patients. In 1943 Chester Keefer¹¹ as Chairman of the Committee on Chemotherapeutic and Other Agents, National Research Council, and his co-workers correlated and reported on the results of treatment by a group of 22 accredited clinical investigators, and the value of penicillin was completely established. It remained to increase production sufficiently to permit the widespread application of the drug to the treatment of infections, both civilian and military. This is now well on the way to final accomplishment.

Production of Penicillin. The cost of producing the early small batches of penicillin was tremendous, but the vital importance of the drug in war medicine has been an ever-present incentive to rapid improvement of methods.

Intensive chemical study has already shown results by improving yield, purity and concentration, and has even lent encouragement to efforts directed toward ultimate synthesis of the drug. At present it must still be prepared by cumbersome biologic methods and, consequently, penicillin is of a more or less variable nature and there is no absolute certainty that different batches will have the same standard activity per milligram of solid material.

The main steps in the production of penicillin are first growing the mold under conditions optimal for greatest yield, separation of the active principle from the mold, and its adsorption and chemical purification and concentration. The solution is then frozen and dried under a vacuum. The dry material is pulverized, assays are conducted to determine the number of units per milligram, toxicity tests are performed, and the powder is finally packaged in a dry state for distribution under the regulations of the War Production Board.

Assay. One of the earliest problems encountered was to determine the strength of penicillin. The cup plate or its variant, the cylinder plate method, and the serial dilution method are the procedures commonly employed. Techniques have been developed by Foster,⁷ Rammelkamp,¹⁴ and Abraham, Chain *et al.*¹ When the latter observers first studied penicillin they prepared a reference standard to be used in evaluating new preparations and, furthermore, they established the Oxford unit (or as it was formerly termed the "Florey" unit) which is defined as "that amount of penicillin which when dissolved in 1 cc. of water gives the same inhibition as this standard." The standard referred to gave a zone of inhibition having an average diameter of 24 mm.

Pharmacology. Florey⁶ found that the penicillin solutions as used therapeutically are bacteriostatic rather than bactericidal. Penicillin is not inactivated by pus, blood, serum or tissue autolysates, and leukocytes and tissues are not harmed by concentrations far greater

than those used therapeutically. Some reactions have been observed, but these seem most likely to be caused by impurities rather than penicillin itself. Those noted have consisted of fever, chills, thrombophlebitis at the site of injection, urticaria, localized tenderness about the site of injection, headache, flushing, tingling in the testes, and muscular pain. Probably the occurrence of such symptoms will become even less frequent as greater and greater purity is obtained.

Hamre *et al.*⁸ found the lethal intravenous dose to be about 90,000 to 250,000 units per kilo in mice, depending upon the purity of the sample. Robinson¹⁸ found that doses of 600,000 units per kilo were not lethal when given intravenously to mice. Such results indicate that further purification, or preparation of the drug as a synthetic chemical substance, may possibly be associated with even more complete freedom from toxicity. There is, of course, some variation in species toxicity, as shown by the fact that acute toxicity is induced in guinea pigs and rabbits with doses that are much lower.⁸ The lack of clinical toxicity of the drug has been one of its most striking characteristics.

Penicillin is rapidly absorbed and quickly eliminated following its intravenous injection.¹⁷ Fifty-eight per cent of it can be recovered from the urine. It diffuses readily through the tissues but does not penetrate the subarachnoid space. Unfortunately penicillin is rapidly destroyed in the gastro-intestinal tract and, consequently, its oral administration is not practical. Rectal administration is also ineffective owing to the inactivation of the drug by coliform bacilli which are thought to act through production of penicillinase. Excretion by the kidney proceeds so rapidly that, following a single intravenous injection, it is often impossible to detect penicillin in the blood longer than 3 or 4 hours. Dawson and Hobby⁴ point out that 90 per cent of the injected material has disappeared in 30 minutes, while the remaining 10% requires 3 or 4 hours before complete elimination. Consequently, single intravenous injections must be given frequently, at least every 3 or 4 hours over the day and night, or administration must be continuous by intravenous drip. Following intrathecal or intraarticular or intrapleural administration, penicillin has been demonstrated for as long as 24 hours.¹⁶ The drug is not normally excreted into the spinal fluid.¹⁵

It is well known that organisms sometimes become resistant to sulfonamides and this likewise is true of penicillin,¹³ but rarely is an organism resistant to both drugs. The action of the two therefore must be fundamentally different, and this may have a practical bearing on therapy of diseases such as chronic osteomyelitis, staphylococcus septicemia and the like. Most of the gram-negative bacilli are resistant.

Indications. In general, penicillin is indicated in the treatment of all infections with gram-positive organisms and gram-negative cocci, but is useless in infections caused by gram-negative bacilli. Consequently it is important to determine the type of organism present. The 500 cases reported by Keefer¹⁶ included many that had failed to

respond to the sulfonamides, including *Staph. aureus* bacteremia and local infections with staphylococci and pneumococci; streptococcal, staphylococcal, and pneumococcal meningitis and empyema; pneumococcal pneumonia; gonococcal infections; and subacute bacterial endocarditis. The results in the latter have been disappointing but, more recently, Loewe *et al.*¹² treated 7 consecutive patients by means of the combined administration of penicillin and heparin with uniformly successful sterilization of the blood stream and relief of clinical manifestations.

Administration. Penicillin is very soluble and under aseptic conditions may be dissolved in sterile water, or preferably in cold sterile normal saline solution, so that the final concentration is from 5000 to 20,000 units per cc. The solution should be kept cold in the refrigerator at all times, and the material to be used as soon as possible after dilution, at the longest within a few days. Further dilutions are made from the ampoule according to the route of administration and the dose to be given. For systemic effect injections should be intravenous or intramuscular, as subcutaneous administration tends to be painful. There is no general agreement as to the best method of administration, as indicated in the recent articles.^{2,4,9} Local infiltration of solutions having concentrations of from 100 units to 1000 units per cc. has not caused enough pain and discomfort in the present series to interfere in any way with the use of the drug.

In general, the published work seems to indicate that much more material is required for treatment by intramuscular or intravenous routes than is the case when the drug can be given topically (this includes intraarticular, intrathecal and intrapleural administration). My own personal observations thus far have shown the desirability, and sometimes the necessity, for local administration directly into the infected area, and when this has been possible, recovery has been more prompt and has occurred with much lower dosage.

Dosage. Penicillin is so soluble that as much as 100,000 units can be dissolved in 1 cc. In general, dosage ranges between 30,000 and 100,000 units daily, depending upon the type of infection. It has been helpful to test out the sensitivity of the organisms wherever possible, and in any event it is essential to know with which organism one is dealing. Recently, there has been less tendency to begin with large initial doses, and often only the first dose is given intravenously, although some observers still prefer to administer at least the first 24 hour treatment by intravenous drip. Dawson and Hobby⁴ emphasize that the first dose need be no larger than subsequent doses, and that larger doses are not necessary in the presence of bacteremia and in cases without bacteremia. Lastly, in general sepsis and for local therapy, the intramuscular route is generally recommended.

As yet, complete dosage schedules have not been entirely worked out for all diseases and the amounts given naturally are those which have been found effective in the treatment of cases of that particular class and do not necessarily imply that final conclusions have been reached.

The early material* used was of weak potency, not very pure, and was not regarded as suitable for administration intravenously. Consequently, localized infections were first chosen for treatment and the solutions employed ranged in strength from only 100 to about 250 units per cc. These solutions were infiltrated into the area of infection with considerable success and, even with this early material, several cases made astonishing recoveries. The method seemed particularly useful in the management of carbuncles, and several cases have responded dramatically and, in certain instances, have even gone on to resolution without formation of a slough. As penicillin became more highly purified and available in higher concentrations, cases have been treated by general administration of the sodium salt with good results, although personal experience still indicates the desirability of depositing penicillin directly into the infected tissues where accessible. In some cases of carbuncle, intravenous or intramuscular administration has been inadequate, and supplementary injections by means of a long needle directly into the necrotic mass has resulted in rapid clearing of the lesion. Penicillin requires several hours' contact with the organism to exert its full effect, and mere irrigation is not enough. Where a sinus presents, as in certain cases of osteomyelitis, satisfactory results have been obtained by forcing a few cc.'s into the tissues with a syringe every 3 hours, then preventing drainage by application of adhesive tape. Local injection in this manner seems much more economical than general administration of the drug.

Report of Cases. CASE 1. L. J., age 58, white female, admitted for a discharging infection of the right great toe and foot. Diabetes known since 1936. The infection began several months previously after cutting a thick callus which would not heel. Temperature varied from 97° to 101° F. White blood count, 10,800; urine sugar, 4+; blood sugar, 291; acetone and diacetic acid, negative. Roentgen ray disclosed no evidence of bone destruction. Under conservative management drainage of pus continued but the diabetes was easily controlled by a diet of C-120, P-80, F-100 = 1780 calories, with 15 units of protamine zinc insulin and 10 units of regular insulin, both given before breakfast; later shifted to a mixture of 10 units of protamine zinc insulin and 10 units of unmodified insulin. One month later Roentgen ray showed much more demineralization and an actual destruction of the bone of the adjacent articular surfaces of the great toe and also the sesamoid bone. A recheck in three weeks indicated further progress of osteomyelitis (Fig. 1). Drainage was established surgically by incision over the ball of the foot toward the great toe. No sequestrum was found. Healing of the incision was prompt but there remained three sinuses draining copiously which gave *Staph. albus* on culture.

Course. Penicillin (200 units per cc.) was injected into each sinus every 4 hours, closing the opening with sterile adhesive tape in order to prevent escape of the drug. Although only a few cc.'s total could be infiltrated, drainage ceased within 2 days, one sinus closed and was followed by the second 3 days later. The last sinus persisted for 2 weeks before finally closing, at which time Roentgen ray showed filling in of the bone at the original site of the lesion. The patient was discharged with complete healing. Total dosage, approximately 20,000 units.

* Supplied by Dr. J. M. McGuire, Lilly Research Laboratories. In later cases both the sodium and calcium salts of penicillin have been employed without apparent significant difference in response.

CASE 2.—W. M., age 63, white male, admitted complaining of an infected foot and diabetes. One toe had been removed a year previously for infectious gangrene. There was a low-grade fever. Culture from the draining area was predominantly *A. aerogenes* and *streptococcus* (non-hemolytic); blood sugar ranged from 142 to 165 mg. per 100 cc., while taking a diet of C-190, P-80, F-90 = 1890 calories without insulin.

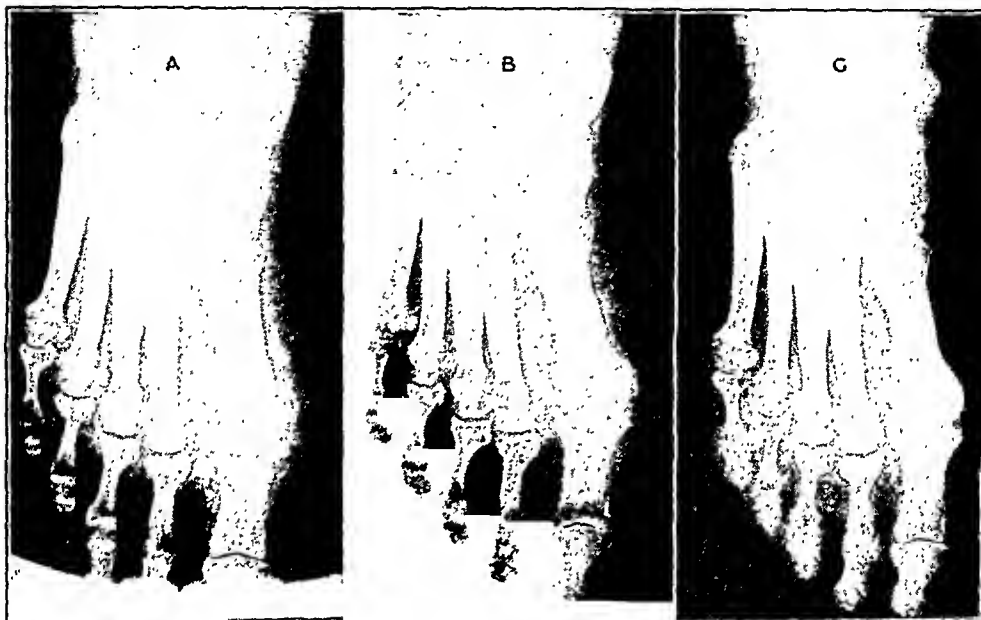


FIG. 1.—Case 1. A, B, Progress of destructive lesion; C, after healing.

Course. The foot was elevated in bed, irrigations with Dakin's solution were instituted and sulfathiazole administered in full dosage. Under this management the cellulitis regressed, but Roentgen ray examinations gave evidence of a destructive bone lesion involving the first metatarsal. Healing did not occur and the sinus continued draining profusely.

Treatment with penicillin (200 units per cc.) was begun by filling the sinus cavity every 4 hours and preventing loss by closing the opening with sterile adhesive tape. At first the capacity was several cc., then gradually the amount lessened as healing progressed. In 2 weeks Roentgen ray showed definite improvement, drainage had ceased, and it was no longer possible to infiltrate appreciable amounts of the drug, so it was discontinued. Complete healing ensued. Total dosage, approximately 30,000 units.

CASE 3.—G. G., age 44, white male, admitted with a large carbuncle of the neck 6 inches in diameter of 1 month's duration. Previous symptoms of diabetes extended only since onset of the infection. Blood sugar, 320 mg. per 100 cc.; urine sugar 4+; acetone and diacetic acid, negative.

Course. Diabetes was controlled by a diet of C-150, P-70, F-100 = 1780 calories, with 40 units of protamine zinc insulin before breakfast and a supplementary dose of 10 units of unmodified insulin. Fever daily ranged to 102° F., the white blood count was 13,000 and there was no response to intensive therapy with sulfathiazole. As the surgical department considered the lesion inoperable, five therapeutic Roentgen ray treatments were administered and were followed by some softening in the center of the lesion which, nevertheless, continued to extend rapidly until it involved the right aural region, the lower part of the face, and produced paralysis of the facial nerve. Blood culture was negative, smears and cultures of the pus showed a mixed growth

*A**B*

FIG. 2.—Case 3. Carbuncle. *A*, Before infiltration of penicillin; *B*, 2 weeks after local treatment with 50,000 units of penicillin.

with *Strep. hemolyticus*, *A. aerogenes*, and gram-positive cocci predominating. The patient was severely toxic and after 2 weeks appeared moribund, with a septic temperature reaching 105° F. (Fig. 2).

A rather crude penicillin solution (about 200 units per cc.) was infiltrated into the necrotic tissue by means of a long needle through the multiple draining sinuses and injections were repeated at 4-hour intervals (20 to 30 cc. doses). Response was prompt and dramatic, the temperature falling to normal within 24 hours. At the end of a week the patient was put in a wheel chair owing to a large decubitus ulcer over the back and sacrum, although he was still very weak and evidenced mental aberration. Softening of the carbuncle occurred rapidly and excess necrotic tissue was removed surgically connecting draining sinuses. The insulin requirement fell to 20 units of protamine zinc insulin once daily. The area on the neck soon filled with healthy appearing granulation tissue (Fig. 2B) but the large decubitus lesion continued to spread and eventually formed a great slough. The patient refused to eat, became progressively weaker and, after being maintained by intravenous infusions for almost two weeks, finally died.

That some of the locally infiltrated solution of penicillin was absorbed generally was shown by finding traces of penicillin in the urine. Had it been available, earlier administration of a suitable concentration for its general effect might well have prevented the ultimate outcome. Total dosage, about 50,000 units.

CASE 4.—C. B., age 43, white female, admitted for furunculosis. A known diabetic for 10 years the patient had received no treatment for 5 years. Four weeks previously she developed multiple furuncles over the back, two of which persisted and had now reached a size of about 1 by 1½ inches in diameter. White blood cells, 4950; blood sugar, 420; urine sugar, 4+; acetone, 1+. Culture from the pointing furuncles disclosed *Strep. hemolyticus* and gram-positive cocci.

Course. Taking a restricted diet, C-120, P-80, F-90 = 1610 calories, the fasting and postprandial blood sugar levels were controlled with 20 units of protamine zinc insulin and 30 units of unmodified insulin before breakfast with 15 units of insulin before the evening meal. All four period urine specimens became negative for sugar and insulin dosage was reduced to 30 units of protamine zinc insulin and 15 units of unmodified insulin, then control was continued with a single injection of a 2 to 1 mixture consisting of 10 units of protamine zinc insulin and 20 units of unmodified insulin in the same syringe. Blood sugar levels averaged 80 units per cc. fasting, 131 units per cc. postprandially.

In this instance penicillin of somewhat higher potency (250 units per cc.) was injected locally into each furuncle three times daily for 8 days. Only 1 or 2 cc. could be injected, but there was rapid and complete regression of the two localized lesions and the patient was discharged completely healed. Total dosage, 12,000 units.

CASE 5. V. T., age 49, white male, admitted for a carbuncle of the neck of 20 days' duration. Sugar had been found in the urine at a previous industrial examination. The "boil" was incised 10 days previously but continued to spread and the lesion was now 18 by 12 cm. with a small skin opening in the center, draining copiously. Blood sugar, 314; urine sugar, 4+; acetone, negative; white blood count, 15,200; temperature, 100.6° F. Pus from the sinus cultured *Staph. aureus*. Retinal examination showed many fresh hemorrhages and typical exudates.

Course. The patient was given a diet of C-120, P-60, F-80 = 1440 calories, and fasting and postprandial levels and the four period urine specimens were well controlled with 30 units of protamine zinc insulin and 15 units of unmodified insulin, both given before breakfast, then doses were transferred to a 2 to 1 mixture of 12 units of protamine zinc insulin and 24 units of unmodified insulin with perfect control. During the interval the patient had a daily chill and elevation of temperature of 101° to 102° F. without positive blood culture. Penicillin (200 units per cc.) in 10 cc. amounts was introduced into

the mass locally three times daily, for 2 weeks. The lesion responded rapidly and healed without any slough whatever. A purplish discoloration was evident over the site of the carbuncle for about a month after discharge from the hospital. Total dosage, 52,000 units.

CASE 6. M. W., age 55, white female, admitted in semistupor, overwhelmed by toxemia, with a carbuncle of the left lower jaw, cellulitis of the face and diabetes mellitus. Temperature was 101° F. on admission, arose to 104°, pulse varied between 100 and 120, and respiration was 30 to 40 per minute. White blood count, 18,500; blood sugar, 320; urine sugar, 3+; acetone and diacetic acid, negative; CO₂ combining power, 56. Blood culture showed positive growth of *Staph. albus* in the first 12 hours.

Course. Penicillin (100,000 units) was administered in saline and dextrose intravenously by continuous drip, on the following day and continued the day after. The cellulitis rapidly spread posteriorly and the patient was obviously moribund. It is interesting that the blood culture became negative after the first 100,000 units of penicillin had been administered. The patient died on the 3d day after admission and autopsy was refused. Dosage, 140,000 units total.

CASE 7. L. B., age 59, white female, admitted complaining of a large painful carbuncle on the back of the neck which had been lanced a week previously and continued to extend. Diabetes was discovered 10 years previously but the patient had never taken insulin. The carbuncle was 6 by 10 cm. in size. There was no fever; white blood count, 9800; blood sugar, 192; urine sugar, 2+; acetone and diacetic acid, negative. Blood culture was negative. Culture from the discharge showed *Staph. albus* and *Strep. viridans*.

Course. Sulfathiazole was administered and the diabetes was controlled with a diet consisting of C-130, P-60, F-80 = 1480 calories and a mixture of 10 units of protamine zinc insulin and 20 units of unmodified insulin, which later was changed to 30 units of clear histone zinc insulin. Fasting and post-prandial blood sugar levels were held within normal limits and the urine remained sugar-free in all 4 daily specimens. Two Roentgen ray treatments were given. Progress was unsatisfactory and penicillin was administered in doses of 5 to 10 cc. (5000 units per cc.) infiltrated directly into the infected tissues through the earlier incision (Fig. 3). This was continued three times daily until 100,000 units had been infiltrated. The lesion was apparently healed but the area was still discolored at the time of discharge, 3 weeks later.

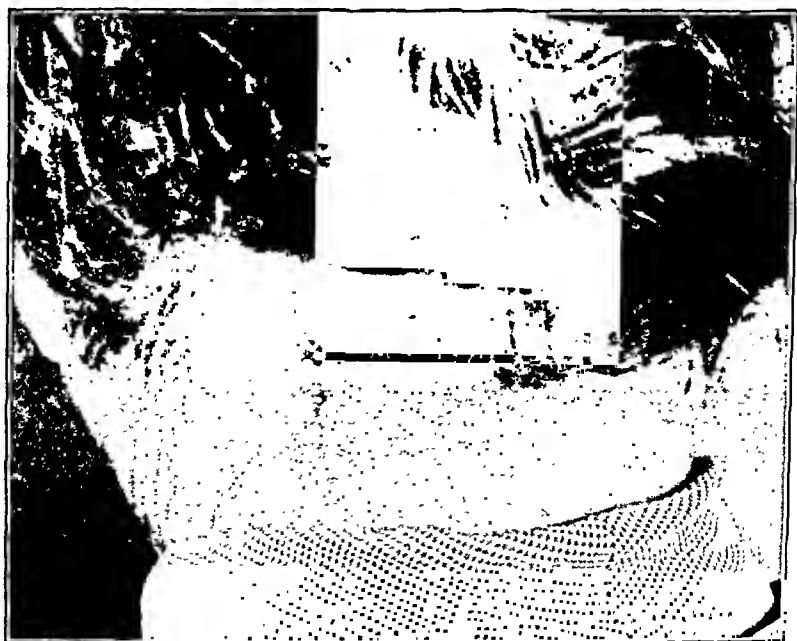
The following week a small fluctuant area was noted above the original site of the carbuncle and it was gently incised to permit drainage. It healed promptly, but during the next week several other small infected areas appeared that seemed to develop in hair follicles. These were treated with sulfathiazole cream, but succeeding crops developed. The patient was readmitted for further treatment, and was given penicillin by intramuscular injections, 20,000 units every 4 hours, then 10,000 unit doses, without any local applications. The reinfected areas subsided promptly and there has been no further recurrence.

This case illustrated the comparative efficacy of locally injected and generally administered doses. If the infection is accessible to local injection, the amount of penicillin required is far less. Total dosage in this case was almost 750,000 units.

CASE 8. R. D., age 61, white male, admitted with a history of diabetes of about 1 year's duration and a carbuncle 11 weeks old. It was a putrid, sloughing, gangrenous mass extending between both shoulders and up to the base of the neck with a deep sinus extending down almost to the spine. Chills, fever, and sweats occurred daily. The blood sugar level on admission was 354, urine sugar 4+, and acetone was positive. Smears and cultures from the pus showed a mixed infection, predominantly gram-positive bacilli and cocci. Blood culture was positive for *Staph. albus*. Serum proteins 5.7 (albumin 2.9, globulin 2.8). The patient was obviously in a terminal state and recovery seemed very doubtful (Plate I, A, B, C).



A.



B

FIG. 3.—Case 7. Carbuncle. *A*, Before treatment with 100,000 units by local infiltration;
B, after treatment. Relapse 3 weeks later.

Course. Administration of penicillin was begun by giving 20,000 units diluted to 1000 units per cc. directly into the necrotic mass, entering through the opening at the center of the carbuncle by means of a long needle. Injections were made every 4 hours until a total of 400,000 units of penicillin had been administered. Progress was dramatic. The fever fell to normal, the necrotic tissues separated in a few days leaving clean granulations behind. One month later after a period of normal temperature when penicillin had been discontinued for several days, there was another chill and the temperature rose to 104°. The original area of involvement showed obvious reinfection, some new localized abscesses formed in the granulation and there was copious, purulent drainage. Another 100,000 units of penicillin was administered intravenously in the 24 hours, followed by 10,000 unit doses intramuscularly every 4 hours until another 100,000 units had been given. It was then discontinued because the patient complained of pain and would not permit further injections. However, there was no further exacerbation, and, although skin grafting was refused, progress continued without interruption until discharge. The blood culture was negative after the initial treatment, indicating that even though the injections were given into necrotic tissues there nevertheless was adequate absorption to produce a general sterilizing effect on the blood stream. Total dosage, 600,000 units.

CASE 9.—J. W., age 69, white female, admitted with advanced infectious gangrene of the left foot, and obvious sepsis. Amputation by disarticulation at the knee joint was performed 1 week later, and was followed by a rather stormy course as there was some reinfection about the site of the incision with purulent discharge, high fever, and finally a slough. After several weeks, a sinus formed over the condyle and there was a copious, serosanguineous discharge showing a mixed infection, and constant low-grade fever. Roentgen ray disclosed demineralization of the condyles and an area of destruction from osteomyelitis.

Course. Penicillin was administered in 20,000 unit doses three times daily. Within 3 days the drainage had entirely ceased and in a week the sinus was completely healed and the area over the exposed condyle was well covered with healthy-looking granulation tissues. One week after beginning treatment the injections were reduced to 20,000 units twice daily and discontinued a few days later. A total of 560,000 units were administered with an entirely successful result.

CASE 10. E. D., age 68, colored female, admitted with a mixed infection of the right foot which was swollen to twice normal size. It was bluish red; there was constant pain; temperature was 101° F.; white blood count, 12,500; blood sugar, 313; urine sugar, 4+; and no acetone or diacetic acid. Roentgen ray disclosed partial destruction of the superior aspect of the proximal phalanx of the great toe and first metatarsal, both areas thought to be the result of osteomyelitis. On account of the widespread involvement and rapid extension of the process, immediate amputation was considered, but it was decided to give the patient the benefit of the doubt, and 4 days later 100,000 units of penicillin were administered intravenously in 24 hours, followed by 20,000 unit doses intramuscularly every 4 hours.

Course. The patient's diabetes responded well to management after beginning penicillin therapy and she was maintained on a diet of C-130, P-60 and F-80 = 1480 calories, with a mixture of 10 units of protamine zinc insulin and 20 units of unmodified insulin given in the same syringe. All four urine specimens were sugar-free with normal fasting and postprandial blood sugar levels. An incision was made to enlarge the area for drainage and at this time the foot resembled a bag of pus about the size of a football. Unfortunately no photograph was taken as we considered the whole affair hopeless. Three days later, under pentothal sodium anesthesia, a large linear incision was made along the side of the foot and drainage was fully established. Fever dropped to an occasional 99° F. and the dosage of penicillin was reduced to 10,000 units every 4 hours. Steady progress was made from that point. Roentgen ray 10 days after treatment was started showed regression of the osteomyelitic

process and actual filling in of the bone. In another 10 days the area of incision was almost filled with healthy granulation tissue, drainage had practically ceased, and with the exception of a small area of necrotic fascia, the wound was clean. This patient received a total of 1,220,000 units of penicillin.

CASE 11. A. McK., age 77, white male, admitted from receiving ward with large carbuncle of neck extending from ear to ear (Plate II, A); temperature ranging 101° to 103° F.; white blood count, 15,050; blood sugar, 301; urine sugar, 4+; and no diacetic acid. Blood culture was negative; the organism identified from pus was *Staph. albus*.

In view of a plentiful supply of the calcium salt of penicillin it was decided to administer only systemic doses, beginning with 20,000 units every 4 hours day and night. Blood sugar levels were satisfactorily stabilized with doses of 20 units of protamine zinc insulin and 10 units of unmodified insulin, both doses given before breakfast. The diet was C-150, P-70, F-80 = 1600 calories. All four period urine specimens were sugar-free and, after the first week, control was maintained with a single dose mixture of 12 units of protamine zinc insulin and 25 units of regular insulin, then 10 units of protamine zinc insulin mixed with 20 units of unmodified insulin.

Course. After 600,000 units of penicillin had been administered, the temperature was normal, but only slight recession of the edges of the lesion was noted. Intramuscular injections were discontinued, and local infiltration of the lesion with calcium penicillin, 10 cc. (1000 units per cc.) was substituted at 4 hour intervals. There was a prompt change for the better. The drug was continued until a total of 932,000 units had been administered, when Plate II, B was taken.

Case 12. A. R., age 26, colored female, had been treated at home for 8 days prior to admission for bilateral lobar pneumonia. She was in severe diabetic coma (severity index, 20); blood sugar, 435; CO_2 , 14; blood pressure, 100/60; pulse, 140; N.P.N., 47; white blood count, 27,000. Initial treatment consisted of $2\frac{1}{2}$ gm. sulfadiazine with the intravenous fluids, then since it was found that she had already been receiving the drug at home, 100,000 units of penicillin was administered in 8 hours.

Course. During the 10 hours the patient was under observation, 320 units of insulin were administered, the blood sugar fell to 267, and CO_2 increased to 19 vol. %. Death appeared to result from sudden cardiac failure.

CASE 13. N. R., age 77, colored male, received penicillin in treatment of a secondary infection of amputation stump, while diabetic control was established with a single dose mixture of 10 units of protamine zinc insulin and 35 units of regular insulin. Fever ranged from 99° to 102° F.; cultures from the area disclosed a mixed infection with gram-negative and gram-positive cocci, and some gram-negative bacilli.

Course. Penicillin was administered intravenously 20,000 units every 4 hours for 2 days; followed by a fall in temperature to normal and marked lessening in drainage. Doses were diminished to 10,000 units every 4 hours, until 430,000 units had been given. Although not healed, the condition of the stump was considerably improved. The insulin dosage was lowered to 10 units of protamine zinc insulin and 30 units of regular insulin mixed.

CASE 14. W. B., age 71, white male, was a mild diabetic easily controlled with a single dose mixture of 7 units of protamine zinc insulin and 14 units of regular insulin, with diet of C-180, P-80, F-100 = 1980 calories. He had a marked perianal cellulitis with a necrotic and gangrenous area extending over the tuberosity of the ischium. Fever ranged to 102° F.; white blood count, 26,600. There was no satisfactory response to full doses of sulfathiazole, and in spite of finding some gram-negative bacilli in the cultures, the infection was regarded as a mixed one, and penicillin, 20,000 units every 4 hours was given intramuscularly to a total of 500,000 units.

Course. The temperature fell promptly to normal, recession of the cellulitis occurred, and recovery was well established within a week. Although healing was not complete, the patient was sufficiently improved to permit transfer to a convalescent home. Carbohydrate tolerance improved and on discharge

the patient was receiving a diet of C-200, P-80, F-100 = 2020 calories, with a single dose of mixture composed of 5 units of protamine zinc insulin and 10 units of regular insulin.

CASE 15. E. D., age 58, colored female, admitted to the ward with a carbuncle situated directly on top of the head, in area 7 by 10 cm.; white blood count, 23,950; temperature 103° to 105° F.; both eyes swollen almost shut. The causative organism was identified as staphylococcus. A diet of C-120, P-60, F-80 = 1440 calories and separate doses of 20 units of protamine zinc insulin and 10 units of regular insulin served to control blood sugar levels and eliminate glycosuria.

Course. Penicillin was given intramuscularly each 4 hours for 10 days, and while the temperature reached normal and the lesion ceased spreading, its size was not much diminished. An incision was made over the dorsum to facilitate drainage, and local injections of penicillin, 500 units per cc., brought about more rapid regression of the lesion. During this interval the diet was increased and control of diabetes was accomplished with a single morning injection of 12 units of protamine zinc insulin and 23 units of regular insulin mixed. Total dosage of penicillin, 800,000 units.

Discussion. It is obvious that with penicillin another great advance has been made in the treatment of certain infections. Penicillin has a few disadvantages as well as advantages, but none of the former are of much practical consequence and the drug is so nearly non-toxic that no one need be afraid to use it. Other than identification of the causative organism no new or difficult technique is involved in its practical application.

In contrast to the sulfonamides, which have been ineffective in the local infections, penicillin is remarkably efficacious. Cases of the infectious type of gangrene, osteomyelitis of the bones of feet, and the huge sloughing carbuncles of the diabetic are amenable to treatment, and adequate supplies to permit immediate application of the drug wherever indicated will undoubtedly result in vastly improved mortality and morbidity rates in the whole group of infections caused by susceptible organisms. It cannot be expected to restore dead tissue, but appears of especial value in the infectious type of gangrene where the circulation is intact. In carbuncles and other infections caused by staphylococci, results have been particularly striking.

In no instance have we observed any tendency toward a deleterious effect on carbohydrate tolerance, nor has penicillin administration necessitated larger doses of insulin. The presence of infection notoriously increases the insulin requirement of the diabetic, but in none of the cases described was there any unusual difficulty, the patients responding particularly well. The 3 deaths in this group of patients cannot rightly be attributed to failure of the drug. One of the carbuncles (G. G., Case 3) received too small a quantity owing to scarcity of material. Case 6 was in the terminal stages of her infection when admitted and undoubtedly had a central lesion. Case 12, in the 8th day of a massive pneumonia complicated by diabetic coma, was in a desperate condition on admission, and died within 24 hours, although making satisfactory progress in recovering from coma.

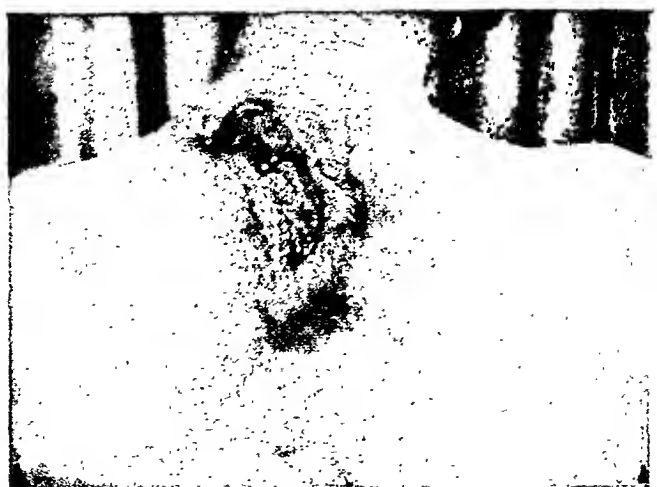
Penicillin should be of great value in the management of certain of the infections so often accompanying or precipitating diabetic coma,



A



B



C

PLATE I.—Case 8. A, before treatment; B, after local infiltration of 400,000 units; C, 5 weeks later.



A



B

since sulfonamides may precipitate in the kidney in an acid urine, and the patient in coma is often in danger from anuria in any event.

Use of penicillin does not relieve the clinician of the necessity for conducting all the other precautions necessary to proper treatment of infections. Drainage must be established surgically as indicated, since the mere administration of penicillin not only is wasteful but may not be adequate. It is essential to determine the causative organism. As experience accumulates, it will be possible to formulate more specific rules of treatment, but it is obvious already that the relatively simple clinical methods available in any hospital can be applied successfully to routine management of this form of therapy.

The rapid and sometimes dramatic response of some of the early cases of carbuncle following the injection of penicillin directly into the infected tissues is noteworthy. In Cases 11 and 15, the drug was given only by intramuscular injection until it became apparent that recovery was progressing only slowly. Almost immediate improvement appeared when injections were made directly into the infected tissues and recovery was established within a few days. The solutions used for this purpose have ranged from 100 to 1000 units per cc. of saline.

Conclusions. Penicillin is an invaluable adjunct to treatment of infections caused by susceptible organisms, and is well adapted for use in the pyogenic infections, such as carbuncles, so frequently complicating diabetes mellitus. Experience in the 15 cases presented suggests that it may be more effective if given locally directly into infected tissues than if injected parenterally for systemic effect. No direct influence on the patient's requirement for insulin has thus far been observed.

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THE TREATMENT OF MENINGOCOCCIC MENINGITIS WITH SULFAMERAZINE*

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SULFAMERAZINE (2-sulfanilamido-4-methylpyrimidine) has been shown to be an effective therapeutic agent, both in experimental infections in laboratory animals⁹ and in clinical infections in man.^{3,6,7} When administered orally, it is rapidly and efficiently absorbed, leading to higher and more sustained blood levels than those obtained with similar doses of sulfadiazine.⁵ Toxic reactions to the drug have not appeared to be more frequent or more serious than those following the use of sulfadiazine.^{2,10}

Recently, we have treated with sulfamerazine a large group of patients with various bacterial diseases;¹ 56 patients in this group had meningococcic meningitis. The purpose of this paper is to report in detail the results in this disease.

Since this study was undertaken, several reports have been published indicating that the use of sulfamerazine in meningococcic meningitis is followed by results as favorable as those obtained by the use of sulfadiazine.^{4,6,8}

Clinical Material. The pertinent data concerning each patient are presented in Table 1.† Forty-one patients were adults and 15 were children 12 years of age or younger. In the adult group, the ages ranged from 13 years to 65 years; 34 were under 40 years of age; only 2 were over 60 years of age. Among the children, the ages ranged from 1 year to 12 years. Four were 2 years of age or younger. The average age for the group was 6 years.

All the patients presented the typical clinical picture of meningitis, and in each case the diagnosis was confirmed by bacteriologic studies. Fifty patients had gram-negative diplococci in stained preparations of the spinal fluid. In 32 of these cases, meningococci were also cultured from the spinal fluid. Positive cultures were obtained from the spinal fluid of the 6 patients in whom no organisms could be identified in stained preparations. Twelve patients had positive blood cultures. Typing of the meningococci which were isolated was not performed.

The severity of the illness varied: 13 patients (23%) were regarded as mildly ill; in 24 (43%) the illness was of moderate severity; 19 (34%) were severely ill. The patients in the last group were either comatose or nearly so. A petechial rash was observed in 34 patients (61%).

Method of Treatment. The usual dosage of sulfamerazine employed in the adult group was an initial dose of 2 gm. orally followed by a maintenance dose of 1 gm. every 8 hours. In children, dosage was calculated on a basis of 1 gm. per 20 pounds of body weight per day. Comatose patients and those who were otherwise too ill or uncoöperative to take medications by mouth were given

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† These patients were treated at the Evans Memorial and John C. Haynes Memorial of the Massachusetts Memorial Hospitals and at the Boston City Hospital.

TABLE 1.—PERTINENT DATA ON 56 CASES OF MENINGOCOCCIC MENINGITIS

Case No.	Age (yrs.)	Sex	Duration of illness at admission (days)	Diagnosis				Treatment				Course (days after beginning treatment)						
				Symptoms and signs				Spinal fluid		Total dose (gm.)	Duration	Av. blood levels mg./100 cc.		Temperature normal	Clinical improvement	Apparent complete recovery		
				Drowsiness	Delirium	Coma	Degree of severity*	White cell count (× 1000)	Smear			Culture	Blood culture				Free	Total
1	24	F	7	0	0	0	+	41.0	+	0	n†	27	11	6	9	4	2	11
2	27	F	1	0	+	+	+++	57.0	+	0	0	21	10	5	6	4	4	11
3	40	M	3	0	0	0	+	18.0	+	0	0	26	9	6	9	2	2	5
4	49	F	30 hrs.	+	0	0	++	0.06	+	+	0	30	11	5	7	2	2	7
5	16	M	2	+	0	0	++	4.7	+	0	0	18	6	6	7	5	2	7
6	13	F	1	+	0	0	+	8.7	+	0	n	17	6	8	9	8	3	7
7	45	M	1	0	0	0	+	7.8	+	n	n	31	10	3	5	6	2	10
8	63	F	1	+	+	+	++++	1.7	+	+	+	40	14	10	14	12	9	12
9	20	F	1	+	+	0	++++	15.0	+	+	0	26	8	8	10	4	2	7
10	37	M	1	+	+	0	++++	2.5	+	+	0	19	6	7	9	7	2	7
11	25	M	1	+	0	0	+	2.5	0	+	n	33	11	9	11	7	2	7
12	38	M	2	+	0	0	++	53.7	0	+	0	31	10	8	10	Afebrile	2	11
13	18	M	1	0	0	0	++	7.0	+	+	+	21	8	5	7	6	2	9
14	15	F	4	0	0	0	+	10.5	+	0	n	28	10	8	11	8	3	12
15	51	M	5	+	+	0	++	2.4	+	0	0	22	8	7	9	4	2	10
16	15	F	3	+	0	0	+	14.0	+	+	+	21	7	12	14	6	2	8
17	15	M	1	+	+	0	++	3.6	+	0	0	20	7	8	10	13	3	14
18	15	F	2	+	+	+	++++	53.0	+	+	0	22	6	10	11	5	2	7
19	18	M	1	0	0	+	++++	5.6	+	+	n	23	9	5	8	4	2	9
20	36	F	1	+	+	0	++++	112.0	+	0	0	25	9	5	7	7	2	9
21	36	M	1	+	+	0	++	1.6	+	+	0	23	9	6	8	5	4	8
22	65	F	1	+	0	0	++	1.1	+	0	+	25	9	8	10	3	3	8
23	16	M	2	+	+	0	++++	34.7	+	+	n	23	7	4	6	4	3	10
24	23	M	1½	0	0	0	+	6.0	0	+	0	23	7	8	10	4	2	8
25	17	M	1	+	0	0	++	7.8	+	0	0	28	10	11	13	2	2	10
26	19	F	1	+	0	0	++	21.7	+	+	0	22	8	5	7	6	2	8
27	17	M	4	+	+	+	++++	Loaded	+	+	n	23	7	7	9	8	4	20
28	30	M	2	+	0	+	++++	17.0	+	0	+	35	9	9	11	9	3	9
29	27	F	2	+	+	+	++++	3.7	+	+	+	20	7	7	9	7	2	10
30	37	F	3	+	0	+	++++	100.0	+	+	0	25	9	3	4	10	4	14
31	25	F	7	0	+	0	++	7.2	+	+	0	20	7	6	8	5	2	7
32	20	M	12 hr.	+	0	+	++	4.0	+	+	0	23	8	8	10	6	3	8
33	19	M	1	+	0	0	++	8.0	+	+	0	20	7	5	7	3	3	7
34	50	M	2	0	+	0	++	9.0	+	+	n	22	7	12	13	5	2	8
35	18	F	1	0	+	0	++	8.2	+	+	0	23	8	6	7	8	2	10
36	16	M	2	+	+	+	++++	Loaded	+	+	0	21	7	5	7	8	3	10
37	17	F	3	+	+	0	++	Loaded	0	+	0	25	9	10	12	9	2	10
38	29	M	2	+	+	0	++	1.9	+	+	0	21	7	8	10	8	3	8
39	32	M	2	+	+	+	++++	Loaded	+	+	+	40	11	7	9	8	2	10
40	23	F	7	0	0	0	++	2.7	+	0	0	34	12	8	10	5	4	12
41	31	M	3	0	0	0	+	0	0	+	0	20	8	n	n	Afebrile	2	2
42	5	F	?	0	0	0	+	11.6	0	+	+	10.5	7	4	n	2	2	5
43	2½	M	3	0	+	0	++++	6.3	+	0	n	30.5	11	8	11	13	2	14
44	11	M	1	0	+	0	++	5.8	+	n	n	20.5	6	14	17	6	3	8
45	9	M	2	0	0	0	+	3.6	+	0	n	19.5	8	7	9	8	3	8
46	1	M	3	+	0	0	+	0.3	+	+	n	8.5	9	8	10	2	2	7
47	11	F	2	0	+	0	++	48.5	+	+	0	20	7	9	11	4	2	7
48	4	F	1	0	+	+	++++	16.7	+	+	+	10	8	11	15	3	2	7
49	2	F	5	+	0	+	++++	15.0	+	+	+	18	11	8	10	7	4	12
50	22	M	1	0	0	+	++	8.0	+	+	n	16.5	10	10	12	12	2	8
51	3 mos.	F	2	+	0	0	++	7.2	+	+	n	11.5	8	12	14	6	2	7
52	7	F	1	+	+	+	++++	9.7	+	+	n	21	8	12	14	4	3	7
53	1½	M	1	+	0	0	++	Loaded	+	+	0	14	10	6	9	5	2	5
54	12	F	1	+	0	+	++++	80.0	+	+	+	19	6	10	12	7	3	8
55	4	F	28 hr.	+	+	0	++	7.2	+	0	0	10	7	12	14	5	2	7
56	11	M	36 hr.	0	0	0	+	7.5	+	+	0	20.5	7	6	8	2	2	7

* + = mild. ++ = moderate. +++ = marked.

† n = none taken.

the sodium salt of the drug intravenously, in doses varying from 2 to 5 gm. A maintenance dose of 1 gm. was given intravenously every 8 hours thereafter, until the patient was able to receive oral medication. Twenty-eight patients (50%) received intravenous sodium sulfamerazine. Fifteen received only the initial dose intravenously. Six patients required intravenous therapy only during the first 24 hours. In 7 the intravenous administration of sulfamerazine was necessary for periods ranging from 2 to 8 days.

Treatment was continued until the patient had made a clinical recovery. The average duration of treatment was 8.4 days. The shortest period of treatment was 6 days, and the longest 14 days. Thirty-three of the patients (59%) received the drug for 8 days or less. The average total dose of drug for the adults was 24.8 gm., with a range of 17 to 40 gm. For children, the average total dose was 16.6 gm. (range of 8.5 to 30.5 gm.).

So far as possible, daily determinations of the whole blood concentration of both the free and total drug were made in all patients. For adults, the average concentration of free drug on the dosage schedule of 3 gm. per day ranged from 3 to 14 mg. per 100 cc., and the average concentration of total drug from 4 to 17 mg. In children, higher levels of both free and total drug were obtained more readily than in adults. Seven children had average levels of free drug of 10 mg. per 100 cc. or more. Only 4 had average levels of less than 8 mg. Only 6 adult patients had average levels of free drug of 10 mg. or over; 17, however, had average levels of total drug of 10 mg. or more.

In all cases, a diagnostic lumbar puncture was performed immediately on admission to the hospital. A second lumbar puncture was performed in most cases on the 7th or 8th hospital day as a guide to the discontinuance of drug therapy. No other lumbar punctures were performed unless signs of increasing intracranial pressure, failure of clinical response, or suspicion of a developing complication made examination of the spinal fluid advisable. In 6 patients who had lumbar punctures during the course of therapy, the concentration of free drug in the spinal fluid ranged from 2 to 5 mg. per 100 cc.

Fluids were administered liberally. The daily intake in most cases was 2000 to 3000 cc. An effort was made to maintain a urinary output of at least 1500 cc. daily. In children, the fluid intake was governed by age and size. Alkali therapy was not used. Sedation, preferably with paraldehyde, and restraints, when necessary to facilitate nursing, were used as adjuncts to sulfamerazine. An occasional patient was given codeine or aspirin for the control of headache.

One patient (Case 2), a 27 year old woman, received 45 cc. of anti-meningococcus serum intravenously on the 3rd hospital day, because of failure to respond rapidly to sulfamerazine. No other patients in this group received antiserum. No other sulfonamide was given to any of these patients, with the following exceptions: One patient (Case 10) received an unknown amount of sulfathiazole a few hours before admission to the hospital; 4 patients (Cases 5, 15, 46 and 50) received sulfadiazine in amounts ranging from 0.3 to 3 gm. prior to admission; 1 (Case 55) received 2 gm. of sulfanilamide intramuscularly prior to admission; 1 (Case 44) received a total of 5 gm. of sulfadiazine on the 2nd and 3rd hospital days. In this case, sulfadiazine constituted one-quarter of the total amount of drug (20.5 gm.) received while in the hospital.

Results of Treatment. During the period of study, all patients who were admitted with the diagnosis of meningococcic meningitis were given sulfamerazine if there was no history of their having received other sulfonamide therapy before entry. In the few cases mentioned in the preceding section, the history of previous sulfonamide therapy

was not obtained at the time of admission. Patients who were known to have received sulfonamides previous to their admission were treated with sulfadiazine. No other selection of cases was made. In this series of 56 patients with meningococcic meningitis treated with sulfamerazine, there were no fatalities.

In 35 patients (62%) definite clinical improvement, usually manifested by a return of consciousness and mental clarity, was apparent within 24 to 48 hours after admission. All but 1 patient showed improvement by the 4th hospital day. One patient remained in coma with an irregular temperature for 8 days despite adequate therapy. She roused suddenly from the coma on the 9th hospital day, and maintained an uncomplicated course thereafter. Fever tended to persist for several days after definite clinical improvement had occurred. The average duration of fever was 6 days. One patient remained febrile for 13 days, and 2 patients were afebrile throughout the course of their illness.

Complications were observed in 8 patients (14%). Arthritis was present in 1 patient (Case 14) at admission, and 2 others (Cases 10 and 43) developed acute arthritis on the 8th and 9th hospital days, respectively. Three patients (Cases 8, 18 and 27) developed facial palsies during the course of treatment. One of these (Case 27) had bilateral involvement. Diplopia was experienced by 1 patient (Case 35) following return to consciousness. The patient in Case 23 was found to have bilateral nerve deafness on the 3rd hospital day. This complication had been suspected before treatment was begun, but could not be proved until the patient had become rational. The facial palsies were improved before the hospital stay was completed. The nerve deafness persisted. The other complications were transient and had disappeared before the patients left the hospital.

TABLE 2.—TOXIC REACTIONS SHOWN BY 22 OF 56 PATIENTS WITH MENINGOCOCCIC MENINGITIS TREATED WITH SULFAMERAZINE

Toxic reaction	No.	%
Nausea and vomiting	3	5.5
Fever	3	5.5
Simple crystalluria	6	10.9
Crystalluria with microscopic hematuria	2	3.6
Microscopic hematuria (without crystalluria)	2	3.6
Gross hematuria	1	1.8
Renal colic	1	1.8
Leukopenia (below 5000)	8	14.5
Granulopenia (below 50%)	2	3.6

Toxic Reactions. Toxic reactions attributable to the drug were observed in 22 patients (39%) (Table 2). Several showed more than one toxic reaction, but in only 1 case was there a serious complication following the use of the drug. Three patients (Cases 2, 23 and 54) developed nausea and vomiting on the 6th day of treatment after doses of 14, 17 and 19 gm. of sulfamerazine, respectively. These symptoms disappeared 3 days after the cessation of therapy. Three patients (Cases 11, 46 and 50) had febrile reactions on the 11th, 9th and 8th days of treatment, respectively.

Crystalluria was a frequent finding, but was not usually associated with hematuria. Eight patients (Cases 19, 23, 30, 35, 36, 43, 47 and 53) developed crystalluria. Of these, Cases 30 and 36 had urine outputs ranging from 1600 to 1800 cc. The remaining cases had outputs of less than 1000 cc. and the crystalluria cleared when the output was increased. Two (Cases 19 and 43) had microscopic hematuria associated with crystalluria, and 2 (Cases 2 and 6) had microscopic hematuria without demonstrable crystalluria. One patient (Case 9) had gross hematuria with renal colic on the 8th day of treatment after receiving 26 gm. of sulfamerazine. The onset of pain in the right flank was sudden. The pain became almost intolerable within 6 hours after it first appeared. A régime of parenteral fluids and sedation was instituted, with complete relief of symptoms in 12 hours.

Eight patients (Cases 1, 9, 16, 17, 18, 20, 25 and 44) while receiving sulfamerazine developed leukopenia. In no case was the decrease in the white cell count sufficiently marked to warrant cessation of the drug. In several patients the count returned to normal before therapy was discontinued. Two of these (Cases 20 and 25) developed a mild granulopenia. Rapid return of the granulocyte count to normal occurred after sulfamerazine was discontinued. There were no cases in this group of drug rash or of toxic symptoms referable to the central nervous system.

Discussion. The results obtained in this series indicate that sulfamerazine is an effective therapeutic agent in the treatment of meningococcic meningitis. The mortality rate in patients treated with antiserum in the 6 year period 1930-1935 in the Haynes Memorial Hospital was 38%. From 1936 to 1940, a 5 year period in which antiserum and sulfonamide therapy were combined, the mortality rate was 45.7%. Part of this high mortality was probably due to the number of cases received from a severe institutional epidemic. In 1941, when various sulfonamides were used and antiserum was occasionally given, the mortality rate was 12.5%.

During 1942 and 1943, sulfadiazine and sulfamerazine were employed exclusively. There were 52 cases of meningococcic meningitis treated with sulfadiazine during this period. Some of these cases, as explained above, were treated concomitantly with those receiving sulfamerazine. Four patients died, a mortality rate in this group of 7.6%. One was moribund on admission and died 3 hours later. Autopsy showed massive hemorrhages into the adrenal glands. Two others died from causes unrelated to the meningitis after they had made a complete clinical and bacteriologic recovery. Only 1 patient, a 53 year old man, failed to respond to adequate chemotherapy, death occurring 27 hours after admission. Excluding all but this last case, the mortality rate in the group of sulfadiazine-treated patients was 1.9%. As already stated, no deaths occurred in the 56 patients treated with sulfamerazine.*

There was no significant difference in the rapidity of the clinical

* Since this study was completed, 3 patients who were treated with sulfamerazine have died. Two of these deaths occurred within 9 hours after the beginning of treatment.

improvement between the patients treated with sulfadiazine and those treated with sulfamerazine. Complications were observed in 15% of the sulfadiazine-treated cases and in 14% of the sulfamerazine-treated cases. The complications were similar in type and course. Toxic reactions to the drug appeared somewhat more frequently in the sulfadiazine-treated cases, 54% showing some toxic response. In general, however, we believe that the incidence of toxic reactions to sulfamerazine differs little from that observed with sulfadiazine.

Summary and Conclusions. 1. Fifty-six patients with meningococcic meningitis were treated with sulfamerazine.

2. No deaths occurred.

3. Complications of the disease were observed in 8 cases. Except for 1 case of nerve deafness, the complications had cleared before the patients were discharged from the hospital.

4. Except for 1 patient who experienced renal colic, no serious toxic reactions to sulfamerazine were encountered.

5. Sulfamerazine is an effective agent in the treatment of meningococcic meningitis.

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THE "MEGA" SYNDROMES

THE COMMON RELATION OF THE VARIOUS MANIFESTATIONS TO THE AUTONOMIC NERVOUS SYSTEM

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THERE is a group of anatomic abnormalities in the alimentary and urologic tracts and in the cerebral ventricular system which, because of their diverse clinical symptomatology and manifestations, have been regarded by most clinical observers as distinct entities apart

from one another. A consideration of their mechanism leads one to correlate all of them in a single inclusive group under the generic term of the "mega" abnormalities.

Idiopathic Dilatation of the Esophagus. Mega-esophagus. Cardiospasm. Idiopathic dilatation of the esophagus is a very rare affliction and is commonly integrated with some form of cardiospasm. Alvarez² found 34 undoubted instances of this abnormality in the records of the Peter Bent Brigham Hospital—an incidence of 1 in approximately 26,000 patients. Modern esophagoscopists have abandoned the old assumption of the presence of some form of obstructive cardiospasm as the cause of the condition as originally suggested by von Mickulicz⁴⁶ in 1882. Instead they integrate this unusual abnormality with a neurogenic incoördination between the lower esophagus and the cardia based upon anatomic or functional disturbances in the autonomic nervous system. This seems to be borne out by the histologic studies of the English school, confirmed by Lendrum²⁵ in this country, which have demonstrated a disintegration of Auerbach's plexus in the dilated portion of the esophagus. This is now generally accepted as the cause of the trouble. This is also corroborated by Knight's²³ work in cats in which he was able to produce experimentally the radiographic appearance of cardiospasm by cutting the vagi to the lower esophagus. Then he was able to overcome the condition by destroying the sympathetic supply through removal of the celiac ganglion. His work frequently is cited now in support of a pathologic disturbance of the autonomic nervous system. However, because this work was not corroborated in dogs by Cannon⁹ and by Vinson, Craig and Moersch,⁴⁷ it has been suggested that the changes in Auerbach's plexus follow the dilatation and stagnation of food rather than act as a cause. However, this assumption seems very illogical to me.

The observable phenomena have been studied roentgengologically by Templeton and Moore.⁴³ In the normal esophagus they describe 3 types of muscular action: (1) a primary wave, a part of deglutition, beginning in the pharynx and traveling down the esophagus; (2) a secondary wave, progressing along the lower half of the esophagus, and (3) a localized contraction which was not peristaltic in character. The lower half of the esophagus undergoes simultaneous contraction, which varies in degree.

In cardiospasm the primary wave, instead of proceeding to the stomach, faded out at the suprasternal notch. In the lower esophagus, peculiar, purposeless, shallow, segmental contractions constantly appeared and reappeared at different levels but strong enough to move the bolus along. They were often accompanied by generalized tonic contractions, which diffusely narrowed the esophageal lumen.

In 3 pathologic specimens, only focal thickening of the muscle fibers was encountered.

While most of the hypotheses implicate an abnormality of the autonomic nervous system, either of pure physiologic function or as the result of organic changes in the sympathetic plexuses of Auerbach, Moschcowitz³⁰ believes that the probability is strong that this is a

mechanism and not a cause. In any event the end result is the same. The question is raised that the organic degenerative changes witnessed in the Auerbach plexus are not primary but secondary to the ever-present inflammatory changes involving the coats of the esophagus in prolonged cardiospasm. In recent years, evidence has accumulated, according to Moschcowitz,³⁰ that primary cardiospasm is psychogenic in origin based upon alterations in the cortex of the brain.

Recently Etzel¹⁴ reported that the disease occurs with great frequency among the poor country people of Brazil. Because of their limited dietary, he believes an inadequate supply of vitamin B₁ may be responsible for the degenerative changes in the intramural portion of the autonomic nervous system. Intensive therapy with the vitamin B complex in the experience of Emery,¹¹ has failed to relieve the condition, so it might seem that if vitamin deficiency is responsible for the nervous disorder, the changes are irreversible.

The case of mega-esophagus reported by Joreg, Borda and Mealla²¹ occurred in a 56 year old man in whom there were dermatologic evidences of pellagra.

Gastric Dilatation. Megastomach. It is common knowledge that in a certain class of individuals there occurs extraordinary accumulations of gastric fluid secretion with associated dilatation of the stomach, frequently to very large proportions. There does not seem to be any particular interference with the motor activity of the stomach; the contractions are normally strong, but always the passage of a stomach tube shows the presence of large quantities of gastric fluid. Commonly this is known as "gastric succorhea."

I do not include here any deviation of the secretory function from the normal which is associated with visible and demonstrable gross lesions of the stomach such as ulcer, carcinoma, etc.

Curiously enough, this occurs most frequently in the female subject and in those in whom there are always elicitable evidences of functional neurologic activity indicating an unstable and easily irritated and disarranged nervous system.

Hypersecretion has been found in cases of chronic appendicitis, and/or in other apparently unrelated forms of intraabdominal pathology. According to Alvarez,³ it has been observed in cases of toxic goiter and in other neurogenic disease. In other instances, it is said to be due to stimuli coming down the vagus nerves.

Pyloric Hypertrophy. Dilated stomachs of this kind in adults are sometimes associated with pyloric hypertrophy in the absence of any inflammatory, luetic, tuberculous or neoplastic lesion. The hypertrophy is centered only in the pyloric muscle.

In infantile pyloric stenosis, the *symptomatology* is of an acute nature and is highly dangerous to life. If no relief quickly follows medical care, the abnormality is corrected by operative division of the pyloric sphincter. This relieves the condition, and follow-up studies indicate the permanence of the relief. I do not know of any instances in which the mega type of stomach has followed.

Saverese⁴⁰ describes the thickening as extensive, grossly visible

and palpable, and involving the entire pyloroduodenal tract. The swelling appears to have a smooth surface; its consistency is hard and fibrous; and it is movable to the normal range of mobility of the pylorus. In less severe lesions the pylorus does not show any external evidence of an anatomic change.

On sectioning, the pyloric wall appears greatly thickened and the thickening involves chiefly the muscular layer of the wall. Microscopic studies by Saverese⁴⁰ show that the inner circular layer of the tunica muscularis is involved especially. The muscle cells are found to be normal as to their arrangement, form, and size. The connective tissue stroma as well as the subserosa and serosa are always found to be normal. Sometimes there is found in the mucosa a leukocytic infiltration which extends also into the muscularis mucosæ and sometimes also into the submucosa.

The various theories to account for this abnormality include: (1) a congenital origin; (2) a spasmogenic origin, and (3) some combination of the two. In any case, the origin seems to be neurogenic.

According to Jordan and Lahëy,²⁰ "The pylorus is notoriously a prominent effector zone for impulses arising from the hypothalamus, its contraction reflecting nervous states and emotional traumas. This is frequently demonstrated by the symptoms of pylorospasm: 'the lump in the stomach,' nausea and vomiting. When the constriction is sufficiently great and enduring, it may be habitual and result in symptoms which simulate ulcer or neoplasm and findings in the roentgenogram which are often indistinguishable from those of an organic lesion."

Megacolon. The manifestations of the congenital form of megacolon (Hirschsprung's disease) are so well known as not to need repetition. Suffice it to say that the patient is usually a large-bellied, otherwise stunted child, in whom an enormous dilatation of the colon is easily demonstrable. The congenital form is characterized by the impossibility of demonstrating grossly any actual or relative obstructing lesion in the terminal segment, either at the point of junction of sigmoid and rectum, or at the anus. The clinical history, any operatively obtained facts, the termination, and any postmortem findings are sufficiently well known to need no repetition here.

Many cases are reported in later life which are classified as megacolic, but it appears from the given description that most of these do not belong to the "mega" syndrome. They seem to be unusual exaggerations of the ordinary forms of chronic dilatation of the large intestine proximal to a definitely obstructing lesion, usually a carcinoma. These should be excluded from this discussion. Two of Rankin's³⁷ cases, reported in 1929, are of this type. His third case is similar, except that here a right colostomy had been present for 2 years.

In Stone's⁴² first case the condition was associated with, or followed an imperforate anus at birth.

In Stone's⁴² second case an old man had an excessively redundant

sigmoid, for which no cause could be ascertained. This man had no great symptoms and no surgery was recommended.

A very different state of affairs existed in the following:

Report of a Case. In March, 1926 this patient, then in the fourth decade of life, had a resection of the sigmoid done. In April, 1928 a resection of the middle portion of the rectum was done. In January, 1929 an ileocecal resection was done. Each resection was done in continuity with immediate restoration of the continuity of the bowel by end-to-end suture. Each resection was done for carcinoma. All of the tumors were histologically similar adenocarcinomata; each tumor had the gross appearance of a primary intestinal growth of this type; and in each there was no macroscopic or microscopic neoplastic glandular involvement, although enlarged glands due to inflammatory change were present. After each of the operations, there was an uneventful convalescence with very prompt healing and with a minimum of hospitalization.

Between each of these episodes, the man was in apparently good health and there were little or no symptoms. The rectal tumor was discovered as a non-symptomatic affair during the course of 1 of his regular follow-up visits. The ileocecal tumor caused a moderate amount of discomfort, which called attention to this part of the intestinal tract. Since 1929, the patient was followed regularly. His general health was excellent and his body functions were carried out in the most normal way and without symptoms or discomfort. This was especially true as far as the intestinal functions were concerned.

In June, 1942 he developed some indefinite abdominal complaints. The physical examination revealed no intraabdominal abnormality and a gastrointestinal series was to all intents normal.

In February, 1943 the patient, while vacationing in Florida, began to complain of increasing abdominal cramps, constipation, nausea, vomiting, and enlargement of the abdomen. The local physician assumed that a mechanical ileus was present and, in view of the history, took it for granted that it was due to a recurrence of the previous malignancy. In the first week of March, when an immediate operation was proposed, because the symptoms, signs, and general physical deterioration of the patient had advanced considerably, the patient left and returned to the city.

When admitted to the hospital on March 11, 1943 the general condition of the patient was still fairly good. He was very much emaciated (probably due to lack of food and to vomiting). The abdomen was distended and a very large loop of gut could be distinguished in the left side of the abdomen. The rectal examination showed a moderate amount of rigidity in the pelvic floor but no malignancy could be distinguished. The rectum was full of feces in spite of the fact, according to the patient's statement, that his bowels had moved daily and that he had passed flatus fairly freely.

Roentgenographic examination (Borrelli) showed an enormously distended colon extending backwards to the ileocolic junction filled with fecal matter admixed with gas.

The picture seemed that of some form of megacolon and it was decided to follow a conservative form of treatment. Following a high compound enema and colonic irrigation, preceded by an injection of prostigmin, a large amount of gas and solid stool was evacuated. This was repeated daily under constant radiographic control with progressively good results both symptomatically and objectively.

By March 15, 1943 the bowel had been completely emptied of stool as was shown in the Roentgen ray observations. An extremely large loop of bowel was now visible in the flat plates occupying the entire left half of the abdomen.

On March 16, 1943 a roentgenographic examination was made by means of a barium enema. This confirmed the previous findings in the flat plates and there was no evidence of any neoplastic growth (Borrelli). This was again confirmed in November, 1943 during one of the follow-up visits.

Uncertainty concerning the etiology and pathogenetic mechanism of megacolon is great and many theories have been advanced for their proper explanation. Alvarez² has pointed out that perhaps the simplest explanation of the ordinary form of megacolon is that, in the particular segment of intestine involved in the process, there has been a failure in development of those neurones in Auerbach's plexus, which are in functional and anatomic contact with the intestinal muscle fibers (Nolfe,³¹ Alvarez^{2,31}).

In the alimentary tract there are 2 sets of plexuses: Auerbach's plexus, which constitutes the peripheral neuron of the parasympathetic system, and is situated between the circular and longitudinal muscular coat; and Meissner's plexus, situated on the inner surface of the circular muscle fibers.

In Auerbach's plexus the fibers of Remak connect the various ganglia and secondary plexuses which are found between the bundles and individual muscle fibers.

Meissner's plexus is formed of small ganglia and their processes form periglandular plexuses and also supply the vascular tissue of the mucosa.

Another type of cell has been described, which is found between the muscle bundles and appears to form some connection between Meissner's and Auerbach's plexuses.

According to Keith,²² the alimentary canal is physiologically divided into a series of neuromuscular sections, each of which is terminated by a zone of sphincteric activity which blocks the passage of the contraction wave from one section into the next. Each of these sections has a special "pacemaker" center, so that in any given section the passage of any contained material can be halted, and such blockage may spread backwards from section to section.

Keith²² distinguishes the following sections: (1) a pharyngeal with a sphincter at the upper end of the esophagus; (2) an esophageal extending to the cardiac sphincter; (3) a gastric ending at the pylorus; (4) a duodenal ending at the duodenal-jejunal junction; (5) a jejunal-iliac section ending at the ileocecal valve; (6) a section containing the ascending colon and the proximal part of the transverse colon; (7) the remainder of the transverse descending and pelvic colon down to the rectum. The terminal sphincter is the one at which the intestinal contents are held up normally.

According to Telford and Stopford, the parasympathetic fibers arise from the anterior roots of the sacral nerves and form a trunk which joins the ventral aspect of the superior hypogastric plexus. They describe two bundles which can be traced to a point where they converge to meet and pass to the left side of this plexus. The small trunk can be followed cephalad to the inferior mesenteric plexus, which it joins distal to the origin of the inferior mesenteric artery. This represents the parasympathetic nerve supply to the distal half of the colon. The parasympathetic innervation of the anal sphincters is derived from the pelvic plexus.

At the present writing it seems to be tentatively assumed that the

parasympathetic influence is excitatory to the colonic smooth muscle and inhibitory to the internal anal sphincter, while the sympathetic system transmits inhibitory impulses to the anal sphincter.

Robertson and Kernohan³⁹ amplified the reports of previous observers in their studies of the plexus of Auerbach in the congenital types of megacolon. They found that the ganglion cells and their connective fibers are definitely smaller than normal; that they were vacuolated; and that the ganglion cells were sometimes absent, or imperfectly formed. On the contrary, in other cases (ulcerative colitis), the ganglion cells and fibers were prominent and even increased in number; and in others (obstructive carcinoma) there were no abnormal changes.

According to Adamson and Aird,¹ the nerves supplying the affected parts of the colon are thicker than normal and the increase is due to a thickening of the epineural tissues rather than to a numerical increase in the contained fibers. That similar connective tissue changes are present in the mesocolon, and in the wall of the bowel, is undoubtedly the expression of secondary effects incident to the chronicity of the abnormality.

The acquired form of megacolon is grossly indistinguishable from the congenital form and here one must sharply differentiate forms of pseudomegacolon. The latter are usually due to obstructing lesions. The former undoubtedly have a similar pathogenetic mechanism as in the true congenital form, even though the primary cause may be entirely different. In the personal case reported here, there is a similar neurogenic mechanism initiated by unavoidable operative division of the same nerve pathways incident to the multiple intestinal resections.

Concomitant and/or Associated Lesions of Megacolon. Many other anatomic aberrations are frequently present in subjects who have congenital megacolon. Excessive elongation of the mesentery (Barth³⁵) and various grades of elongation and redundancy of the colon (Pennington,³⁴ Marfan³⁵) have been reported.

Pennington's³⁴ case included diaphragmatic eventration combined with segmental megacolon and other congenital dystopias.

Segmental neuromuscular defects have been mentioned by Hawkins,¹⁸ Lennander,³⁵ and by Formad.³⁵ I wish to speak especially of optic nerve and ocular lesions and of cerebral and ventricular defects.

Associated Neurologic Abnormalities: A. Optic Nerve and Ocular Abnormalities.

Case Reports. Worcester-Drought and Shafar⁵² report the following experiences in which megacolon was associated with ocular changes:

1. One case associated with retinitis pigmentosa, optic atrophy, and right cataract.

2. A 38 year old woman with central choroidal excrescences and bilateral scotomata; symptoms since the 24th year; diagnosed as subacute intestinal obstruction and partial volvulus.

3. An 8 month old boy with symptoms since premature birth at 8 months; blind; urinary incontinence; some improvement later; bilateral optic atrophy without any neurologic or muscular manifestations. Cerebrospinal fluid and Wassermann negative.

Worcester-Drought and Shafar⁵² cite the following cases from other sources:

4. Wilbuat⁵¹ of Amsterdam: A 17 year old female, disseminated choroiditis; adiposity; enlargement of the sella turcica. Father had similar eye changes.

5. Gurich:¹⁵ Bilateral coloboma of the optic nerve merging with extensive right choroidal coloboma and left total detachment of retina. Other abnormalities included narrow sella turcica; pigeon chest; and mild mental deficiency.

B. Cerebral and Ventricular Abnormalities:

There are instances in the literature in which megacolon has been associated with hydrocephalus. The following are examples:

In one of the cases reported by Worcester-Drought and Shafar⁵² there was present a congenital megacolon and a congenital hydrocephalus. No block in the pathways of the cerebrospinal fluid was observed in the encephalograms, the air passing into and filling the ventricular system and being visualized in the subarachnoid space over the cerebral hemispheres.

In a case reported by Watts and Uhle,⁵⁰ congenital megacolon was associated with recurrent episodes of Jacksonian epilepsy. Encephalography showed an enlarged ventricular system equal on both sides.

Hydrocephalus. Congenital hydrocephalus is frequently accompanied by other abnormalities of the central nervous system, such as spina bifida, encephalocele, and so on, or by abnormalities elsewhere, *e. g.*, clubfoot, syndactyly, and so on. The anatomic and clinical picture is well known; the widely dilated ventricles containing a liter or more of fluid; the obliteration of sulci and convolutions and the atrophy of the cerebral tissue to a mere thin bag; the corresponding dilatation of the entire ventricular system; and the corresponding changes in the brain case. In the great majority of the cases there is no demonstrable obstruction in any part of the ventricular system.

The combination of hydrocephalus and other congenital abnormalities, both in the central nervous system and elsewhere, is not uncommon. The association with megacolon is striking. The possibility presents itself as to whether the interference with the development of the brain by the expanding ventricular system can in any way be correlated with dysfunction of the autonomic nervous system which appears adequately to account for the megacolon. The site of the disturbance may lie in the peripheral, ganglionic, or central portions of the autonomic nervous system.

The available data are as yet insufficient to say definitely that autonomic elements exist in the cerebral cortex. But various gastrointestinal disturbances preceding, accompanying, or replacing focal epileptic seizures are now thought to emanate from a cortical level (Penfield and Gage, 1933).³³

Experimentally, Bochefontaine (1876)⁸ associated stimulation of the sigmoid gyrus with intestinal movements. The observations were experimentally confirmed by Bechterew and Mislawski (1890);⁷ by Beattie and Sheehan (1934);⁶ and by Watts and Fulton (1934),⁴⁹ who removed the premotor area from the cortex from both hemispheres in the monkey and produced intussusception with fatal intestinal obstruction. This could never be obtained after severance of the vagi. Mettler²⁸ and his co-workers (1936) removed the frontal lobes bilaterally and caused hyperactivity of the stomach and pyloric spasm, while

similar disturbances of motility were produced by removal of one or of both cerebral hemispheres.

Morbid hunger has been encountered in cases of cerebral tumor, and Levin (1936)²⁶ described in a group of children an interesting syndrome consisting of periodic attacks of somnolence and morbid hunger which he considered as possibly being due to a corticothalamic derangement. Previously (1932), Cushing¹⁰ had made the observation that experimental lesions anywhere in the intracranial course of the tracts leading from the anterior hypothalamus to the vagal centers were liable to give rise to ulceration and perforation of the stomach.

It seems, then, that there is considerable evidence to support the existence of cortical and hypothalamic centers which control the activities of the autonomic nervous system. It is conceivable that an embryologic defect, attributable to, or associated with hydrocephalic expansion of the ventricles, might cause changes in these higher centers and secondary effects in the Auerbach plexuses farther down, and consequent derangement of intestinal motility and so result in megacolon. It must be admitted, however, that no definite proof exists at present as to a central origin of Hirschsprung's¹⁹ disease. Further observation is necessary to discover the primary seat of the neurogenic disturbance in congenital megacolon. Nevertheless, the accumulated data is more than suggestive.

The "Mega" Syndrome in the Urologic Tract and Its Association With the "Mega" Syndrome in the Alimentary Tract.—Megacolon is commonly associated with disturbance of bladder function and the latter becomes the prominent feature in many cases.

1. *Chronic Bladder Dilatation*—"Mega" Bladder. The association of unusual and extraordinary dilatation of the bladder has been noted by a number of observers.

Telford⁴⁴ stated that he has observed infrequent urination and a huge thin walled bladder in association with megacolon.

Richer's³⁸ case is a very typical example:

In a 50 year old woman there was a sudden attack of retention of urine, the bladder reaching to the umbilicus and containing several liters of fluid. Continued catheterization over a period of 1 month was not followed by any improvement. Then attacks of intestinal colic called attention to an enormous coëxisting dilatation of the entire colon.

There were no signs of tabes or other motor or sensory lesion of the central nervous system. The spinal fluid was negative. No cause was found on physical and laboratory examination and on roentgenologic examination by barium enema for the colonic dilatation. No particular effect was observable after treatment. Richer³⁸ rightly assumed that this was a case of coëxisting "mega" enlargement of both bladder and colon.

Richer³⁸ mentions another case without giving any details occurring in an 18 year old girl who presented herself because of the presence of a megacolon and in whom there was also present "considerable retention of urine."

Cases have been referred to by other observers. In these typical cases the only abnormality of the bladder is its unusual size, permitting remarkably infrequent urination with the voiding of large quantities at one act.

In none of these cases can the condition be regarded as atony of the bladder, since in all the detrusor muscle was capable of powerful contraction. It seems that there is dysfunction in the vegetative nervous supply of the bladder.

The nerve supply of the bladder includes: (a) the sympathetic system (chiefly the presacral nerves); (b) the parasympathetic system (the pelvic nerves), and (c) the pudic nerves.

The pudic nerves are thought to be of somatic origin, but they may possibly transmit also impulses of involuntary type, although this is ordinarily the function of the autonomic nerves.

All three of these sets of nerves contain both afferent and efferent fibers.

The modern conception of the innervation of the bladder contains both anatomic and physiologic observations and is based on the work of Learmonth.²⁴ Simons and Emanuel⁴¹ accept the imbalance idea of the innervation of the bladder until it is thoroughly disproved and they feel that there is much in the researches of Barrington⁴ to substantiate this stand. The imbalance theory of bladder innervation is that the sympathetic and the parasympathetic distribution of the thoracolumbar and sacral outflows to the bladder are antagonistic and balance each other to a certain extent.

The general plan of the autonomic supply to the bladder is very similar to that in the colon. The parasympathetic branch carries contracting or emptying stimuli, while the sympathetic branch controls the bladder sphincter.

Both Watkins,⁴⁸ Entz, and Haymond¹² express the opinion that the nature of this bladder abnormality suggests strongly that it is analogous to and is the nearest counterpart to congenital megacolon.

2. *Megalo-ureter*. This bladder abnormality (megalo-bladder) may exist alone or it may be associated with similar general dilatation of the ureter (megalo-ureter) and kidney pelvis (megalo-pelvis). There are fairly numerous examples in the literature and in one's practice. I do not refer to solitary or multiple cysts of the kidney, which specimens exhibit a lining membrane, and are within the kidney substance. They are not connected with the urinary excretory tract, but in all cases there is also evidence of embryonal developmental changes in the kidney parenchyma. I do not refer to various forms of dilatation at the lower end of the ureter, usually included under the terminology of "ureterocele." These, too, nevertheless, are most commonly of congenital origin.

According to Morison,²⁹ localized spasms occur in the ureter which are usually intermittent in character. The spasms occur either in the entire extent of the ureter or they are restricted to certain zones in which there is normally a physiologic narrowing (pelvo-ureteral zone, the crossing of the common iliac vessels, the zone of the broad ligament in the female or of the vas in the male, and the transmural zone). The spasms give rise to pain which is referred to definite areas of the abdomen. In long-standing cases, submucous and interstitial changes follow. To my mind, these spasms seem to correspond to pyloric

spasms, or to spasms which are frequently seen in various corresponding strategical zones of the large intestine. It seems most likely that all of these forms of spasms have a common neurogenic origin.

3. *Megalopelvis (Hydronephrosis)*. Latent hydronephrotic distention of the kidney, without apparent clinical signs, occurs in 50% of the cases, and is revealed only by some complication or by various bizarre clinical syndromes, which can be classified as follows:

1. Chronic syndrome: (a) a dyspeptic form which simulates gastric or pyloric tumor; (b) an enteritic form which simulates mucomembranous enteritis, and (c) a form of "chronic appendicitis" which is encountered most frequently.

2. Acute abdominal syndromes in which the hydronephrosis can simulate intestinal occlusion or peritonitis.

It is interesting to list the "intrinsic" causes which are assumed to precede these renal urologic dilatations. I am indebted to Mathé²⁷ for this very complete classification:

1. Congenital:

(a) Congenital *per se*.

(b) Associated with the following anomalies of the kidney and ureter:

- (1) Bifid pelvis and ureter
- (2) Double pelvis and ureter
- (3) Abnormal insertion of the ureter
- (4) Horseshoe kidney
- (5) Ectopic kidney
- (6) Fused kidney
- (7) Abnormal outlet of the ureter
- (8) Aberrant distribution of the blood-vessels
- (9) Stricture of the valve formation at the ureteropelvic junction

2. Acquired:

(a) Renal ptosis associated with obstructive bands, kinked ureter, and aberrant vessels

(b) Lithiasis

(c) Renal torsion

(d) Stricture of the ureteropelvic junction

(e) Stricture of valve at the ureteropelvic junction

(f) Tuberculosis

(g) Tumors of the cortex, pelvis, and ureter

(h) Aneurysm of the renal artery

(i) Pyelonephritis

(j) Interstitial nephritis

(k) Neurogenetic causes; neuromuscular dysfunction, and sympathetic cotonia

3. Traumatic:

(a) Late sequel of trauma to the cortex, pelvis, or upper ureter

(b) Following surgical interventions

(1) Pyelotomy

(2) Ureterotomy

(3) Ureterostomy

(4) Surgical injuries to the ureter itself due to cutting, clamping, or tying of the ureter during operation on other organs.

Considering the "intrinsic" cases of hydronephrosis, one group of investigators thinks that the greater majority of causes are obstructive phenomena. I am, personally, in complete agreement with the opposing group who believe that numerous cases of hydronephrosis

(megalopelvis) are congenital in nature. Bazy⁵ was the first to insist on the congenital nature of hydronephrosis (megalopelvis—Bazy's disease), pointing out the fact that megalopelvis and megaloureter often exist since birth and are often associated with megalocolon, diverticula of the esophagus, etc. The opinion (Papin,³² Mathé²⁷ *et al.*) is gaining ground that this congenital anomaly (megalopelvis) occurs much more frequently than was previously supposed or realized; that it exists at, and develops progressively from birth onwards, both because of the original anomaly and because of other subsequently appearing factors; that stones associated therewith are secondary to preëxisting stasis; that accessory vessels and high insertion of the ureter are without significance and/or result from the pelvic dilatation; and so on. These additional factors occur only when considerable damage has preceded. If we accept this viewpoint, the term hydronephrosis is misleading and should be reserved for other types of renal distention. The term "megalopelvis" seems much more appropriate.

Harrison's¹⁷ cases undoubtedly belong in the congenital group. It is very suggestive that supposed correction of "structural abnormalities" such as "stricture" and "vesical neck obstruction" did not relieve the condition nor influence the final outcome. The causal relation of these anatomic abnormalities must, therefore, be considered questionable.

One of the cases cited by Mathé,²⁷ of which a photograph is presented, is a typical hydronephrotic distention of the kidney (megalopelvis) in which the kidney tissue has apparently disappeared entirely, and in which a stone is present in a lower pocket. Mathé²⁷ remarks, that the "stone is secondary to preëxisting stasis rather than being an etiological cause. . . ."

This is a typical example in the experience of almost everyone. I have seen several of such cases in my own practice and in the hospital experience of my colleagues.

The picture is almost always complicated by infection. Other factors then come into play, especially calculus formation, and the clinician usually attributes the pathogenetic mechanism and the resulting clinical picture to the infection as the primary and/or most important cause. This, of course, is an erroneous assumption.

The Relation of the "Mega" Abnormalities to a Neurogenic Pathogenetic Mechanism. In each of these anatomic localizations, the "mega" abnormality, described herein, has this phenomenon in common: that in each an extraordinary accumulation of the normal fluid and/or solid content of each takes place. In each case, the thought usually runs to the relationship of secreting and excreting phenomena, the net disturbance of which results in the extraordinary accumulation and the necessary consequent distention. This thought results in the current conceptions regarding the pathogenetic origin of the disease.

Nevertheless, from the accumulated evidence, it seems that this factor is of little importance in the pathogenesis of the cases in the alimentary tract, and in the megabladder and megaloureter cases, but

is of more importance in the megalopelvis and in the megaventricle (hydrocephalic) cases.

In the alimentary canal, the fibers of the sympathetic system corresponding to the derivatives of Meissner's plexus are known to ramify around the secreting glandular structures in the wall of the viscus. They undoubtedly influence the secretory activity of these glandular cells and the assumption is not far fetched that, in the general disturbance of neurologic function, an increased activity of the secreting mechanism takes place which adds to the general picture. This has special reference to the gastric cases, and possibly to the renal cases.

The thought goes further in considering the sympathetic supply of the appropriate part of the vascular network. Some part of the increased accumulation of fluid might be due to increased blood supply related to extraordinary activity of the nerve plexus and a consequent dilatation of the vascular channels. This activity finds its greatest field, most probably, in hydrocephalic accumulations (increased blood supply and secretion in the ventricular ependyma).

There seems to be much more pathogenetic importance in the neuromuscular dysfunctions of the sympathetic system. In most of the instances this is of congenital origin. In a few cases, it follows trauma (operative or other) in which the same result follows a mechanical (division of nerve paths) interruption of normal nerve impulses.

Neuromuscular dysfunction, so called "sympatheticotonus" occurring in lesions of the autonomic system can cause atonic relaxation of a hollow viscus or dilatation because of any relative obstructing spastic ring muscle. Both pathologic processes result in dilatation and finally in an atonic condition.

Atony of a hollow viscus is never primary. It is caused either by abnormal innervation, by obstruction, or by both factors. Continuous intraviscus retention from any cause will produce atony of the muscular wall. In some cases it is difficult to determine which factor is primary. With most cases, atony and obstruction are inextricably combined; and in muscular lined viscera, a certain amount of hypertrophy precedes the final relaxation. In a parenchymatous organ (kidney, brain), atrophy follows with disappearance of the cellular elements.

Irritation or paralysis of the sympathetic splanchnic or pelvic ganglions, and so on, can cause atonic changes in the kidney pelvis (Mathé);²⁷ in the ring muscle of the ureteropelvic junction (von Lichtenberg), and in the major and minor renal calyces, in the lower esophagus and cardia (Alvarez,^{2,3} Lendrum,²⁵ Knight²³) and at the pylorus (Alvarez,^{2,3} Saverese).⁴⁰ This results from overstimulation of the sympathetic nerves (Harris and Harris);¹⁶ or, as other evidence seems to show, rather from an uncoördinated and badly integrated action between the opposing activities in the sympathetic system of nerves.

The factors involving sphincteric dysfunction in a hollow organ are: (1) imbalance of innervation, with predominance of the sympathetic or filling nerves; (2) rigidity or failure of adequate relaxation of the internal sphincter referred to as dysectasia; (3) apparent failure of coördination of segmental reflexes involved in the normal act of empty-

ing of the viscus referred to as achalasia; and/or (4) a disturbance of the suprasegmental or cerebro-spinal reflex.

There is evidence to make one believe that functionally and mechanically the root of the difficulty is failure of time correspondence and coördination between an approaching contraction wave and relaxation of the sphincter fibers at one or more of the strategic points. Hurst has invented the term "achalasia" for this functional incoördination with special reference to the pyloric sphincter. The adult variety of acquired megacolon is explained in this way by Etzel,¹³ and he points out that the case of mega-esophagus and of otherwise unexplainable extraordinary forms of gastric dilatation owe their production to this mechanism. Etzel¹³ also integrates this functional disturbance with destruction or malformation of Auerbach's plexus.

The sphincters are normally in a state of normal contraction, and sympatheticotonus makes their relaxation difficult, thereby setting up a more or less continual spasm resulting in increased tone of the muscle fibers. This leads to increased intravisceral pressure, dilatation and delayed emptying time with extraordinary intravisceral accumulations with no mechanical obstruction. According to von Lichtenberg,⁴⁵ this disorder is by no means rare in the renal cases, making up 59% of 80 cases of hydronephrosis operated by him; and he has often demonstrated this muscular contraction during operation.

While these viewpoints were supplied by Mathé²⁷ to the urologic mechanism, their applicability to the alimentary canal seems unquestionable to me; and it is most noteworthy that von Lichtenberg⁴⁵ compares neuromuscular dysfunction in the urologic apparatus with cardiospasm and pylorospasm for which he assumes a like mechanism.

The conception seems unavoidable that the various observable clinical phenomena of the "mega" syndrome in the different anatomic localizations are, in reality, manifestations of a general disease, the essential basis of which is a neuropathy of the autonomic nervous system. This finds its inception most commonly in congenital abnormalities of physiologic function or structure and are followed subsequently, as the disease continues, by more pronounced or newly developed anatomic changes of definite character.

In other cases, the phenomena appear in early adult life and continue. It seems that in these there are abundant evidences of instability of nervous functional activity, in which irritability and emotional outbursts are characteristic. These cases occur most commonly with the lower esophagus and cardia cases and with the pyloric cases. This group has important relationships with psychosomatic medicine, a clinical segregation which is increasing in extent as our knowledge of this comparatively new branch of medicine accumulates.

In other cases of non-congenital origin, this form of neuromuscular dysfunction or incoördination or both, sometimes follows trauma. The personal case described above belongs in this category inasmuch as the condition followed operative trauma. In the traumatic cases, the dynamic upset of physiologic function undoubtedly corresponds to mechanical interference with the carriage of nerve impulses or with

their proper integration in the physiologic purpose by division of nerve pathways. I believe that in these cases there is no relation to obstructive phenomena.

Summary. The alimentary and urologic tracts and the cerebral ventricular system are occasionally the seats of malformations which resemble one another to the extent that a dilatation of the contained cavity occurs, varying from moderate to most extraordinary extent. Commonly there is a single localization of the abnormality. Less commonly several localizations exist either in one or in more than one of these systems. Commonly other congenital defects and deformities coexist. While this is most often a congenital manifestation and appears at, or can be traced directly to the time of birth from which point it progressively develops, rarely, similar gross anatomic changes are observable later in life which cannot be so integrated; which occur apparently spontaneously in the absence of obstructive phenomena or which follow some operation in which a radical change is unavoidably produced in the normal anatomy (postoperative megacolon cases).

The factor of secretion seems to play either no rôle or at most an indifferently contingent or adjuvant part, or both, in the production of this abnormality in the alimentary and urologic tracts. In both of these localizations the available factual knowledge seems to indicate an exact similarity in the pathogenetic origin and mechanism. This is most commonly a neuromuscular deficiency and dysfunction, characterized by faulty integration of nerve impulses, so that there is incoördination between an approaching contraction wave and the necessary relaxation of a functional or anatomic sphincteric arrangement at a strategic point. Sometimes this is a purely functional disturbance. At other times it is based upon anomalous or deficient anatomic structure centered in the autonomic nervous system, either in the ganglionic cells (Auerbach's plexus) or in their connecting nerve pathways. The cases are of congenital origin, in which instance there are at times some indications of disturbance in the higher autonomic centers. In a few cases there is a traumatic origin and then the mechanism is a local one.

In the hydrocephalic cases (megaventricle) the factor of secretion seems important. When the megaventricle is associated with megacolon, it seems that the atrophic changes in the cerebral cortex involve higher autonomic centers which, in turn, seem to be integrated with changes in the lower autonomic centers (plexus of Auerbach), and the megacolon then follows.

In the lower esophagus, cardia and pyloric cases there is evidence of the presence of unstable nervous functional activity. In some of these there seems to be some connection with psychosomatic medicine. When there is marked gastric succorhea with the extraordinary gastric dilatation ("mega" stomach), the ramifications of the nerve fibers derived from Meissner's plexuses around the secreting lands in the stomach mucosa seems to indicate a pathogenetic relationship between the two.

While all of these differ markedly in their manifestations in accord-

ance with their localizations and with any added or complicating factors, they show general similarities in the resulting architecture of the affected part. There are frequent neurologic complications. They involve pathogenetically the same part of the nervous system. And they seem to have a similar pathogenetic mechanism. All of the facts lead one to suspect and assume an origin in the autonomic nervous system. It seems appropriate to include them all under the generic term of the "mega" syndrome.

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THE PROTEIN CONTENT OF EDEMA FLUID IN PATIENTS WITH ACUTE GLOMERULONEPHRITIS

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MOST textbooks of medicine state that acute glomerulonephritis is a diffuse disease of the body capillaries and that edema occurs as the result of widespread capillary damage. It is pointed out that the edema fluid in acute nephritis contains a high concentration of protein and that to account for this the capillaries must be injured and abnormally permeable to protein. Examination of the data available in the literature reveals that only a few determinations of the protein content of the edema fluid in acute nephritis have been made and that the methods used are open to criticism. It seemed worth while, therefore, to measure the protein content of edema fluid of additional patients with acute nephritis. If this fluid contained a high concentration of protein it might be assumed that generalized capillary damage was at least in part responsible for the edema. If the protein concentration were low this explanation for the edema would not be tenable.

Methods. Edema fluid was obtained from patients with acute glomerulonephritis by inserting several 23-gauge needles into the subcutaneous tissue of an edematous portion of the body. They were left in place for not more than 5 minutes. From time to time the local tissue pressure was increased by stretching the skin of the part. The needles were removed and the fluid in them collected in fine glass capillary tubes. The size of the sample was obtained from the difference in weight of the filled and empty capillary tube. Only a few milligrams of fluid were necessary for analysis. The fluid was examined under the microscope without removing it from the capillary tube. If it was cloudy, or contained a large number of red blood cells, the specimen was discarded. If there were only a few red cells, the specimen was accepted, because experience showed that the protein concentration of the fluid was not significantly affected by a small number of cells. At the same time blood was obtained for the determination of the total protein nitrogen and non-protein nitrogen contents of the serum. The total nitrogen content of the edema fluid was determined by a modified micro-Kjeldahl procedure with nesslerization and colorimetric determination by a photoelectric colorimeter.⁶

Results. Determination of the protein content of edema fluid was carried out in 10 patients with acute glomerulonephritis (Table 1). All were children or young adults who developed classical acute nephritis with generalized edema, hypertension, and hematuria. In none was there a history of previous renal disease. In most instances the acute nephritis followed an upper respiratory infection; in 2 patients it occurred as a complication of scarlet fever. In most of the persons studied the onset had been relatively abrupt and was moderately severe. None of the patients died during the acute illness, and in all instances there was almost complete recovery during the period of hospitalization, as evidenced by subsidence of symptoms and disappearance of the urinary abnormalities. During the acute stage of the disease some of the patients had moderate cardiac enlargement and pulmonary congestion, as determined by Roentgen ray examination. There were no complicating diseases which would have been expected to produce a serious alteration in the serum protein level.

TABLE 1.—SUMMARY OF OBSERVATIONS ON SUBCUTANEOUS EDEMA FLUID IN 10 PATIENTS WITH ACUTE GLOMERULONEPHRITIS

Patient	Blood serum		Protein content of edema fluid	
	Non-protein nitrogen, mg. per 100 cc.	Total protein, gm. per 100 cc.	Leg gm. %	Sacral region, gm. %
1	41	5.8	0.4	
2	33	6.5	1.0-1.1	
3	63	6.1	0.2-0.3	0.5-0.7
4	198	6.3	0.1-0.3	
5	34	5.8	...	0.8
6	..	6.5	...	1.0
7	54	5.8	0.1	
8	24	5.2	0.1-0.2	
9	..	6.4	...	0.9-1.0
10	30	4.9	0.3	
Average	..	5.9	0.4	0.8

In 7 patients edema fluid was obtained from subcutaneous tissues of the leg. The average protein content of this fluid was 0.4 gm. % with extremes of 0.1 and 1.1 gm. %. In 4 patients the fluid was from the subcutaneous tissue in the sacral region. The average protein content of this fluid was 0.8 gm. % with variation from 0.5 to 1.0 gm. %. In 5 instances 2 or more samples were obtained from the same patient and in none was the variation in protein content more than 0.2 gm. %. There was no apparent correlation between the serum protein and non-protein nitrogen levels of the blood and the protein content of the edema fluid. The average serum protein concentration in the 10 patients was 5.9 gm. per 100 cc.

Comment. The average value of 0.4 gm. % for the protein content of the edema fluid from the legs of these patients with acute glomerulonephritis is considerably lower than previously recorded. The subcutaneous edema fluid of the legs in patients with cardiac failure contained an average of 0.2 gm. % of protein.⁷ Thus, the protein concentration of the edema fluid of the legs in acute nephritis and in cardiac failure showed no significant difference. The protein content of the fluid from the sacral region in the patients with acute nephritis averaged 0.8 gm. %. In patients with cardiac failure who

had no lowering of the plasma protein concentration, the protein content of the fluid from the subcutaneous tissue of the sacrum averaged 0.6 gm. %.⁸ Again there was no significant difference between the protein content of the edema fluid of the sacral region in patients with congestive heart failure and those with acute nephritis.

In acute nephritis, edema is not usually extreme and, in general, the procuring of samples of edema fluid is much more difficult than in conditions where fluid retention is more pronounced. When obtaining fluid for analysis, the needle must not be left in place too long or else local capillary damage will occur, and almost pure blood serum will be obtained. In none of our cases was the needle left in place longer than 5 minutes. As a check on the validity of the method used in such patients with minimal amounts of edema, additional studies were carried out on patients with cardiac failure. Samples of edema fluid were obtained from patients with massive edema. Fluid flowed freely as soon as the needle was inserted. Later, after most of the edema had been reduced by either elevation of the part or diuresis, samples of edema fluid were again obtained. This time fluids had to be forced into the needles by raising the tissue pressure by local pressure. No significant difference was found in the protein content of the fluid under the different conditions.

The condition of the skin and subcutaneous tissues must be known in order to evaluate the significance of a high protein concentration in edema fluid. If the area is inflamed, the edema fluid will always contain considerable protein. It is possible that the protein content of subcutaneous edema fluid in post-scarlatinal nephritis may be higher than in patients who have not had any reaction in the skin. It is of interest that the edema fluid of the leg which had the highest protein content was from a patient with post-scarlatinal nephritis.

Although general statements regarding the protein content of edema fluid in acute nephritis are common, reports of analysis of edema fluid are rare. Beckman¹ studied 4 patients with acute glomerulonephritis. The edema fluid protein content in 3 patients was 1.12, 1.12 and 2.52 gm. per 100 cc., while in the fourth repeated observations ranged from 1.12 to 1.96 gm. per 100 cc. The protein content was determined by a refractometer. Peters and Van Slyke⁵ mention 1 case of acute nephritis in which the protein concentration of the edema fluid was 0.1 gm. per 100 cc.

The data presented here are not compatible with the thesis that the edema of acute glomerulonephritis can be differentiated from that of congestive heart failure by study of the protein content of the edema fluid. There seems little reason to believe that the edema is primarily dependent on an increase in capillary permeability. Edema which is caused by a sudden marked increase in capillary permeability should be associated with hemoconcentration. Acute nephritis is not accompanied by hemoconcentration. Indeed, in the cases reported in the literature⁴ and in the 2 patients in this series on whom the data were obtained, the hematocrit reading rose as the edema disappeared, indicating that in the edematous state there was hemodilution rather than hemoconcentration. An opportunity to observe the changes in

the hematocrit reading when the capillary permeability is suddenly increased, occurred during the study of a patient with widespread giant urticaria resulting from the previous administration of horse serum. The fluid in urticarial wheals is known to have a high protein content, demonstrating that the capillaries are abnormally permeable to protein. A few hours after the onset of the urticaria the hematocrit reading was 46. Several hours later at the height of the reaction it was 49. Four days later, after the urticaria had subsided, the reading was 36. The edematous state was accompanied by hemoconcentration, and hemodilution occurred as the urticaria subsided. This is the reverse of what is observed in acute nephritis.

The simplest explanation for the presence of edema in acute nephritis is that the fluid intake exceeds the fluid loss from the body, because of a disturbance in renal function. The extracellular fluid content of the body is increased and edema results. The retained extracellular fluid is deposited throughout the tissues in areas where the capillary pressure is high or where the tissue pressure is low. When the patient is upright the excess fluid accumulates in the part of the body below the heart, because the capillary pressure there is elevated by the effect of gravity. On lying down, the capillary pressures throughout the body become more nearly equal, the excess fluid reenters the blood stream and is redistributed throughout the body in accordance with the dictates of tissue pressure. Burch² has shown that the formation of edema in the tissues usually results in a rapid rise in tissue pressure, with the result that the rate of transudation into the tissues is slowed. The tissues of the eyelids were unusual in that edema formation caused little rise in tissue pressure. When fluid is redistributed with the patient recumbent, the eyelids swell rapidly, because in this area the edema formation is unopposed by a rising tissue pressure.

The thesis that the accumulation of edema about the eyelids at night is caused by the easy distensibility of these tissues, rather than by diffuse capillary damage, is supported by observations on patients with chronic constrictive pericarditis. These patients may become edematous before they have any orthopnea. If they are able to lie flat in bed at night, edema of the eyelids may be present when they awake. During the day, when they are sitting or standing, the edema of the lids disappears and edema of the lower extremities can be detected.

Patients with acute nephritis may develop congestive heart failure. LaDue³ has shown that in acute nephritis with edema the venous pressure is elevated and the transverse diameter of the heart is increased. He believes that heart failure, with its increased venous pressure, accounts for the edema. Data previously presented from our clinic has shown that in chronic congestive heart failure the retention of salt and water is dependent on a disturbance in renal function secondary to the failure of the heart.⁹ The edema fluid would be expected to have the same protein concentration regardless of whether the renal dysfunction is the result of kidney damage from the nephritis or the result of altered renal physiology from heart failure. The degree of changes in the kidney, as seen under the microscope, and the knowl-

edge that retention of fluid may be the cause, rather than the result of the rise in venous pressure,⁹ support the thesis that primary renal damage is the chief factor causing salt and water retention. It is difficult to believe that cardiac failure alone is responsible for the striking oliguria seen in certain patients with acute nephritis, though heart failure undoubtedly plays an important rôle in certain instances.

Summary and Conclusions. The protein content of edema fluid in 10 patients with classical acute glomerulonephritis has been determined. In 7 patients in whom edema fluid was obtained from the leg, the average protein content was 0.4 gm. %. In 4 instances, when the fluid was obtained from the sacral region, the average protein content was 0.8 gm. %. These values do not differ significantly from those obtained on the edema fluid of patients with congestive heart failure studied by similar methods.

The evidence at hand indicates that the cause of edema in acute nephritis is water and salt retention secondary to a disturbance in renal function, and not the result of diffuse capillary damage throughout the body. The method of study is not suitable for determining whether the retention of salt and water results from the pathologic process occurring in the kidney or from heart failure, as suggested by LaDue. The extensive pathologic changes seen in the kidney in acute glomerulonephritis support the view that the altered renal function is caused by these pathologic changes, rather than by altered renal physiology because of failure of the heart.

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OBESITY AS A CLINICAL PROBLEM

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STATISTICS based upon standardized death rates indicate the apparent wisdom of avoiding obesity.¹⁰ The increased mortality rate in the obese group is associated with a higher incidence of cardiovascular

diseases. The present study seeks to define, in part at least, the complications associated with obesity, and to review the experience of a large clinic with attempts at weight reduction. The effect upon hypertension of a change in body weight has been investigated. A search has been made for possible etiologic factors of obesity in disorders of the central nervous system and of the endocrine glands.

Materials. Patients and records of the Metabolism Clinic of the New Haven Hospital have been selected for study. The obese group, 141 in number, consisted of 54 women who weighed 180 to 200 pounds, and 87 patients of both sexes who weighed 200 to 484 pounds. The latter included 62 females and 25 males; 63 of these patients weighed 200 to 250 pounds; 17 were in the 250 to 300 pound group; 7 others weighed between 300 and 484 pounds. A few patients who were large rather than obese were not included in this study. One hundred non-obese patients selected at random from the same clinic served as controls. The population of this clinic includes all diabetics in the entire out-patient department, all patients with known or suspected disorders of the thyroid and other endocrine glands, all cases of glomerulonephritis and many cases with other types of renal disease, and various nutritional disturbances. The last group includes many individuals referred for therapy of obesity and study of possible endocrine factors. It also serves as a follow-up clinic for a portion of the patients with urinary tract infections and for some of the patients with a history of toxemia of pregnancy (Table 1).

TABLE 1.—PRIMARY DIAGNOSIS IN OBESE AND CONTROL SERIES

	Obese	Control
Diabetes	73	61
Obesity	41	
Hyperthyroid	11	14
Myxedema	1	2
Goiter	4	1
Renal disease	3	17
Toxemia	5	3
Hypometabolism	1	1
Hypermetabolism	1	
Basophilism	1	
Steatorrhea		1
Total	141	100

After a preliminary survey certain conditions were selected for detailed study. The presence or absence of diabetes mellitus, varicose veins, gall bladder disorders, joint symptoms, and vascular disease was noted in all subjects. The effects of weight change on hypertension could be analyzed in 41 of the patients in the obese group. The records of attempts at therapeutic reduction were adequate in 67 subjects over a sufficiently long period to permit some judgment of the results.

Criteria for Symptoms and Diseases. The diagnosis of diabetes mellitus was based on the usual criteria of hyperglycemia and glycosuria. The presence of varicose veins was recorded only if the patient had either extensive varicosities, varicose ulcers, a history of thrombophlebitis, or of surgical treatment of varicose veins. Slight, clinically insignificant, superficial varicosities were not included. Diagnosis of disease of the gall bladder was based on roentgenographic evidence of cholelithiasis, a history of colic with acholia and jaundice, or a record of a surgical procedure upon the gall bladder. Gastro-intestinal symptoms alone, no matter how suggestive, were considered inadequate evidence. The presence of discomfort, pain, or swelling in the joints of the lower extremities was noted. Asymptomatic roentgenographic changes in the joints were not recorded, unless actual complaints were offered by the patient. A few cases of generalized arthritis have been excluded from both the obese and

control series. The diagnosis of vascular disease was based upon any of the following: (a) Persistent hypertension of 150/100 or higher, (b) unequivocal cardiac enlargement by teleoroentgenogram, (c) congestive failure beyond a history of exertional dyspnea, (d) retinal hemorrhage, exudation, scar formation, or pronounced sclerosis of the vessels, (e) albuminuria greater than 1+, (f) formed elements in the urinary sediment in abnormal numbers, (g) marked electrocardiographic changes.

Results. Figure 1 represents the age distribution of obese and non-obese subjects and the incidence of certain disorders in these 2 groups.

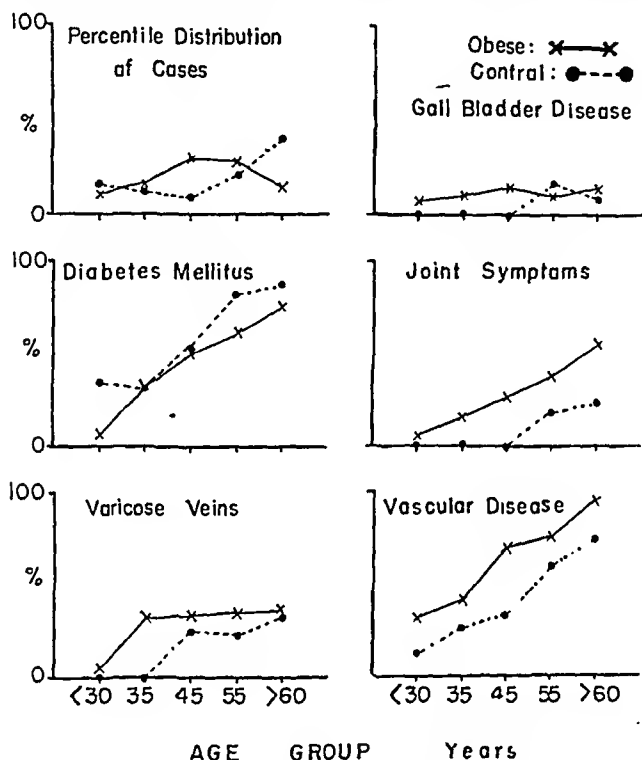


FIG. 1.—Percentile distribution of obese and non-obese subjects according to age and incidence of symptoms and disorders. The groups 35, 45, 55 consist of subjects 30 to 40, 40 to 50, 50 to 60 years of age respectively.

Age. The infrequent occurrence of obesity after the 6th decade suggests a dissociation between obesity and longevity.

Diabetes Mellitus. The high incidence of diabetes mellitus in both groups reflects the specialized composition of the clinic population, and therefore the use of these statistics to study the relationship between diabetes mellitus and obesity is not valid. The basic difficulty lies in the fact that all patients with diabetes attend this dispensary, while only certain overweight patients are referred to this clinic for treatment. It is to be noted, however, that the presence of diabetic patients in approximately equal proportions in the overweight and normal weight groups obviates the possibility that differences between the 2 groups can be ascribed to the diabetic state.

Varicose Veins. These occur about as frequently in both groups beyond the 4th decade, but they appear a decade earlier in the obese

group. Since only clinically troublesome varicosities were included, this represents an important complication of obesity. The changes with obesity which result in varicose veins are not known. In this group, varicose veins occur more often in the male patients than in the female, so that pregnancy cannot be the basic factor responsible for the higher incidence in the obese subjects.

Gall Bladder Disease. The total number of cases of gall bladder disease is not high in either group. This may be in part an expression of the exacting criteria for this diagnosis. Nonetheless, just as with varicose veins, there is an appreciably higher incidence of gall bladder disease among the younger obese subjects. This difference disappears after the 5th decade.

Joint Symptoms. The overweight patients in all age groups are especially apt to complain of pain in the joints of the lower extremities. It is not possible to state, of course, whether obesity produces changes in articular and periarticular tissues as a result of increased pressure, or whether the extra weight serves merely to make minor changes clinically significant. The latter appears to be more probable, since objective findings in the joints are but rarely encountered.

Vascular Disease. Unquestionably diseases of the cardiovascular system are found much more often in overweight patients of all age groups. Hypertensive and arteriosclerotic diseases predominate. Diabetes mellitus occurs a little more often in the control group (61 in contrast to 50%), and hence cannot be correlated with the higher incidence of vascular disease in the obese group. Actually, the inclusion of patients with diabetes mellitus masks an even greater difference in the 2 groups, rather than explains the actual results. Furthermore, the control group includes an unusual number of non-obese patients with nephritis, so that the proportion of patients with vascular disease is unduly high. If these were excluded, the 2 lines of the graph would be further separated.

Hence it is apparent upon comparison of overweight and control groups, each of which contains approximately the same proportion of patients with diabetes mellitus, that obesity is correlated with a decreased life expectancy and is associated with a higher incidence of joint symptoms, gall bladder disease, varicose veins, and cardiovascular diseases. All of these disorders tend, in addition, to appear earlier in the overweight group.

Effect of Obesity Upon Blood Pressure. This study afforded an opportunity to test the general belief that obesity predisposes to the development of hypertension, and that hypertension can be affected favorably by weight reduction. Figure 2 represents graphically changes in the weight and in the systolic blood pressure of 41 obese subjects.

In 12 of 23 patients with hypertension the systolic blood pressure decreased 20 mm. of mercury or more as the weight fell. In 9 others the hypertension was either unaffected or progressed further. In the remaining 2 patients the pressure increased while the weight remained constant. The diastolic pressure followed the systolic in direction of

change, but the order of magnitude was usually less. It is possible that the remission in some of these would have occurred spontaneously.

It is interesting that only a moderate reduction in weight, 10 to 40 pounds, occurred in all but 1 of the patients whose pressure fell. Although it is recognized that the use of a sphygmomanometer too narrow in relation to the arm circumference results in false high values, most of the patients lost too little weight to alter arm diameter significantly. Indirect evidence of the unimportance of arm size in relation to change in blood pressure is obtained from an analysis of the patients with normal pressure who gained weight. Twelve patients increased in weight by 15 to 93 pounds and not one developed a blood pressure beyond 150/100. Only 2 of the 14 patients initially without hypertension reached hypertensive levels as they gained weight. In

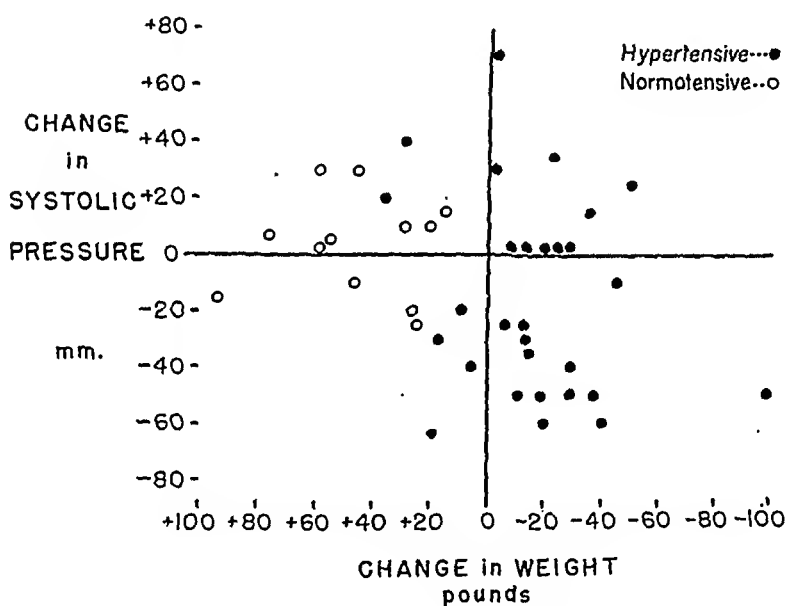


FIG. 2.—Effect of change of weight on the systolic blood pressure.

4 others, who already had hypertension, the pressure fell toward normal despite an increase in body weight. It is apparent that the levels of blood pressure and of weight are not closely correlated. Although hypertension was present more frequently in the obese patients, a gain of weight was rarely productive of hypertension, and a loss was correlated with a drop in pressure in about one-half of the cases. The latter finding is particularly significant in view of the usual progressive course of hypertension.

It is not possible to state that, if these patients had never become obese, the development of vascular disease could have been avoided. The higher mortality in the overweight group suggests that obesity exerts an unfavorable influence upon vascular disease once it has appeared. This study indicates that one manifestation of vascular disease, hypertension, can be minimized in some patients by reduction

of weight. It should be remembered, however, that the level of pressure is of less importance than the state of the vascular system as a whole. Hence a decrease in blood pressure, when obtained, cannot be interpreted as evidence that the unfavorable mortality associated with obesity has been canceled.

Therapy. Adequate records were available of the attempts at weight reduction in 67 of the 87 patients who weighed 200 pounds or more. In diabetic patients the diet was restricted in calories with definite stipulation of the proportions of carbohydrate, fat, and protein. In the others the daily intake included at least 70 gm. of protein. The calories varied from 1000 to 2000, with 1200 the most frequent prescription. This was distributed among 3 or more feedings. The patient was instructed by an experienced dietitian and then seen at intervals of 2 or more weeks. Seven patients received thyroid medication without acceleration of the weight loss.

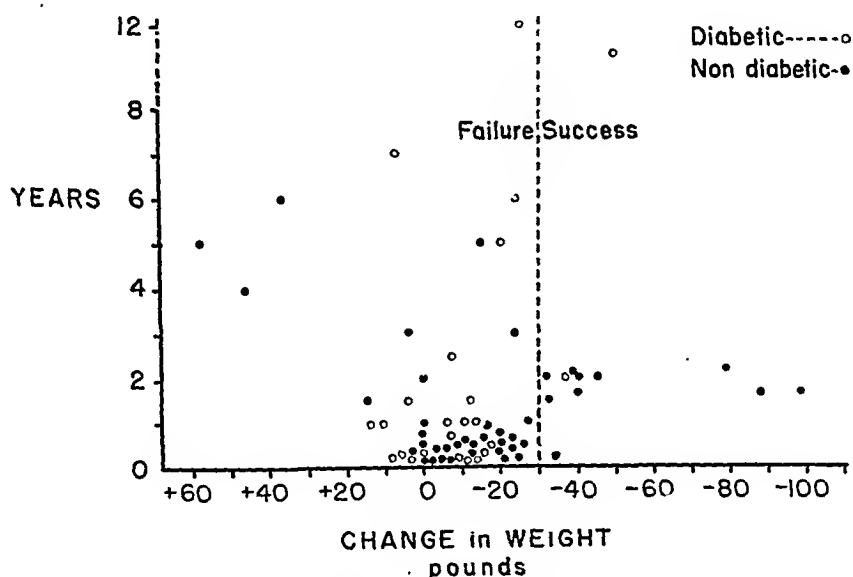


Fig. 3.—Results of attempts to reduce permanently the weight of 67 obese subjects weighing 200 to 484 pounds.

The results of treatment are presented in Figure 3. Of the 67 patients, 19 failed to reduce their weight or actually gained, and 12 others lost less than 10 pounds. The weight of 24 patients decreased 10 to 30 pounds during intervals of several months to 12 years. Only 12 subjects lost 30 pounds or more. Of these, 11 had not relapsed at the end of 2 years or longer. No information was available concerning the subsequent course of the 12th patient. If reductions of 30 pounds or more without subsequent relapse are considered significant in patients who weighed 200 to 484 pounds, therapy was successful in only 1 of every 5 obese subjects. Temporary reductions of weight are not included in the group treated successfully. It is possible that some of the patients who were reduced successfully after 2 years of observation will relapse ultimately. These might well be replaced,

however, by patients in the 10 to 30 pound weight loss group who reduced their weight further. It is rather surprising to find that the greatest reductions were recorded in the non-diabetic group, since more continuous attention to the diet might be expected from the diabetic patient. This may be partially explained by the fact that most of the extremely obese people were not diabetics. Our criteria of success demand a permanent reduction. By this standard the program employed for reduction failed in about 80% of the cases. The reason for this high proportion of failures deserves consideration.

Discussion of Results of Therapy. Since the laws of thermodynamics unquestionably apply in obesity,^{9,12} weight control necessitates adjustment of the caloric intake and expenditure. All obesity results from eating more food than is needed by the body. Social habits, hereditary elements, nervous and endocrine factors may all be present, but they are effective only insofar as they stimulate excessive appetite or reduce caloric expenditure. It has been demonstrated repeatedly that a negative caloric balance will eventually result in a loss of weight,⁸ although at times this may be masked temporarily by retention of water.⁷ Why then has therapy been successful in only a few patients?

Most writers, in describing successful treatment of obesity, present largely results of short-term studies.^{3,4,5,6,8} Only one other attempt at long-term statistical evaluation of results has been found.¹¹ In this group three-fourths of the patients eventually regained most of the weight lost initially. Short-term studies neglect the fact that weight reduction must be permanent, if the complications of obesity are to be avoided or minimized. In accordance with the criteria for success adopted in this study, a relapse canceled a previous loss in weight. It is possible, furthermore, that our results would have been better with a less obese group. Certainly a loss of 10 to 30 pounds, considered a failure in our patients with marked obesity, would be proportionally much more significant in subjects weighing less than 200 pounds.

Failure must be ascribed to an inability to change permanently the dietary habits of the patient. This does not appear to be a consequence of hypothalamic lesions of the type which have been produced experimentally in rats, monkeys and dogs, with resultant obesity if free access to food is allowed.^{1,2} Careful scrutiny of records and patients has revealed only 11 cases of disorders of the nervous system of all categories in a total of 141 patients. This infrequent finding can hardly be proposed as an explanation for a persistent habit of overfeeding, even if it were assumed that all these lesions involved the diencephalon. Neither can responsibility for failure to reduce weight be relegated to disorders of the endocrine system. The patients with thyroid dysfunction who attend this clinic fall into the control rather than the overweight group. Out of a total of 25 patients with myxedema now under observation in this clinic, only 1 is obese.

The rôle of economic factors in failure to adhere to the diet is difficult to evaluate. Patients who attend the dispensary are often unable to provide for themselves a separate reducing diet. Many of them are housewives constantly exposed to the temptation of food.

It is possible that under more favorable circumstances some of these patients could reduce their weight. On the other hand, similar difficulties are frequently encountered in our experience with office patients in better economic circumstances. Apparently some individuals, irrespective of economic status, prefer the pleasures of overeating to the advantages of a normal nutrition.

It might be thought that the problem of obesity is one of diminishing importance under present conditions of food rationing. This does not, however, appear to be true. The excess calories are obtained from an increased consumption of carbohydrate foods. It must also be remembered that many of the meats now available contain a high proportion of fat.

Since moderate restriction of calories fails to produce permanent weight reduction in so many cases, alternative modes of therapy and types of diet deserve consideration. Increased exercise and thyroid medication can be dismissed briefly, for our experience with their futility coincides with that of others.^{4,8} Sporadic exercise usually stimulates the appetite out of proportion to the small increase in total caloric output. Desiccated thyroid in moderate amounts has little effect on the metabolism of euthyroid individuals, since the hormone is inactivated.¹⁴ With larger doses, undesirable symptoms of hyperthyroidism appear, and the effect of the increased appetite cancels the higher caloric output.

Both lower and higher caloric diets have been used in the treatment of obesity. Marked limitation of intake to a diet yielding only 400 or 500 calories daily has been advocated.^{3,5} This régime naturally results in more rapid loss of weight than do the 1200 or 1400 calorie diets. If sufficient protein is included, a negative nitrogen balance can be avoided.¹³ This program, however, can be followed for only comparatively brief periods.¹¹ Evans, a leading exponent of this régime, presents only the amount of weight lost acutely. In a recent report he notes that 121 patients lost on the average 21.7 pounds in 8 weeks.⁵ Comparable results were obtained with our régime during the initial acute period. The high percentage of failure in our cases and the apparent success of other clinics can be explained by differing criteria. We have defined success in terms of permanent weight reduction rather than in terms of ability to lose weight acutely. It has already been pointed out that if the complications of obesity are to be avoided, the weight reduction must be permanent. Relapses are common following periodic drastic caloric limitation, just as they are with the more moderate régime. The reports of Newburgh⁸ and of Evans^{3,5} present no data permitting statistical evaluation of the permanency of their results. In selected patients, however, such a régime may produce satisfactory weight control.

A less marked restriction of calories to about 2000 daily offers a rational alternative plan of therapy, since caloric expenditure of most patients is higher. Under this plan an ordinary diet is prescribed, altered sufficiently to produce a small negative caloric balance. Weight decrease is then slow and continues over a long period of time. Reduction is accomplished through the inculcation of correct eating habits

rather than through a régime which cannot be long continued. It does seem to be true that in those who reduce successfully by this gradual method, subsequent control is facilitated.

In this clinic no correlation has been found between the number of calories in the assigned diet and the permanency of the weight reduction. Immediate success was common with almost any régime containing 2000 calories or less, if the diet was followed. This is represented graphically by the large number of patients who lost up to 30 pounds during periods of several months (Fig. 3). Ultimate success was much more rare. It must be recognized that a diet which is metabolically sound fails in a great many cases to produce any lasting correction of the obesity. Too much attention to immediate success obscures these poor ultimate results. Less emphasis ought to be placed upon calories and more upon the dietary habits of the patient, so that over a sustained period the intake will remain less than the expenditure of energy. The procedure by which a particular patient is to be persuaded to alter his habits of eating must necessarily be individualized.

Summary and Conclusions. 1. The complications associated with obesity have been studied in 141 obese subjects and compared with those in 100 control subjects.

2. An unusually high incidence of varicose veins, of joint symptoms confined to the knees and ankles, and of hypertensive cardiovascular disease was found in the obese group, particularly in subjects less than 40 years of age.

3. In obese patients with hypertension, the blood pressure fell in approximately one-half of the patients as the body weight was reduced. Hypertension usually did not appear in obese individuals as their weight increased further.

4. The experience of a large metabolic out-patient department with attempts at weight reduction has been reviewed. Success, based upon a permanent weight loss of 30 pounds or more, was obtained in only a minority of the cases.

5. Reëducation in basic eating habits is essential for permanent reduction. The actual daily negative balance of calories is of much less importance.

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NUTRITIONAL IMPROVEMENT OF CHILD MENTALITY*

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MENTAL energy is a product of 2 factors—capacity and intensity; the one is determined by heritage and maintained by essential nutrients, especially proteins, lipids, water and anions, while the other factor depends on immediate availability of dextrose, oxygen, vitamins and cations. Metabolic disorders affecting the capacity factor or brain structure tend to produce irreversible anatomic lesions, while nutritional disorders affecting cerebral function tend to produce reversible biochemical lesions. The rôle of some essential nutrients has been evaluated in the mental activity of experimental animals but the applicability of this knowledge to children is a moot question. Since multiple nutritional deficiency predominates, the pertinent problem is to determine the effect of malnutrition on retarding mental function.

Despite the difficulty of evaluating the nutritional status of children at various ages and the task of excluding underlying diseases affecting mental growth, we have, nevertheless, been able to study the effects of nutritional improvement on child mentality in 182 children from 2 to 9 years of age, half institutionalized at the Fifth Avenue Hospital and New York City Children's Hospital and half out-patients at the Heckscher Institute and at the Senior Author's office.

TABLE 1.—EFFECT OF NUTRITION ON MENTALITY

	<i>Malnourished Groups</i>			
	41 retarded		50 normal	
	Range	Average	Range	Average
Age	2-8 yrs.	3 yrs. 10 mos.	2-10 yrs.	4 yrs. 8 mos.
I.Q.	20-90	45	95-145	110
Interval	1-7 yrs.	3½ yrs.	1-3½ yrs.	2 yrs.
I.Q. change . . .	-8 to +44	+10	-12 to +55	+18
<i>Well-nourished Groups</i>				
Age	2-8 yrs.	4 yrs. 10 mos.	2-10 yrs.	5 yrs.
I.Q.	20-90	52	95-140	110
Interval	1-8 yrs.	3½ yrs.	1-3 yrs.	2 yrs.
I.Q. change . . .	-20 to +11	-0.3	-25 to +20	-0.9

Group 1 included 41 mentally retarded and 50 normal children malnourished at the time of the first mental test and well nourished at the time of the second test. Group 2 included 41 retarded and 50 normal children, well nourished at the time of the first test and still well nourished at the time of the second test. Each group was equated for chronologic age, I.Q., and interval between Kuhlmann-Binet or

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Stanford-Binet tests. The data in the tables below reveal an average rise of 10 points for retarded and 18 points for normal children of Group 1 in contrast with an average of zero change for the retarded, and a -0.9 change for the normal in Group 2. The greater variability shown by higher standard deviation of I.Q. in Group 1 in comparison with Group 2 is probably due to the initial variations in nutrient deficiency and individual responses to nutritional therapy. The significance of this difference in I.Q. change in favor of the malnourished group is 2.43, indicating that chances are 99.2 in 100 that the difference is greater than zero.

TABLE 2.—I.Q. CHANGES IN MENTALLY DEFICIENT CHILDREN

<i>Malnourished Group</i>			
	Range	Average	Standard deviation
Age	2 yrs. 1 mo. to 7 yrs. 10 mos.	3 yrs. 10 mos.	1 yr. 5 mos.
I.Q.	22 to 82	45	16
Interval	8 mos. to 7 yrs.	3 yrs. 7 mos.	1 yr. 6 mos.
I.Q. change . . .	-8 to $+44$	$+10$	12
<i>Well-nourished Group</i>			
Age	2 yrs. 7 mos. to 7 yrs. 7 mos.	4 yrs. 10 mos.	1 yr. 5 mos.
I.Q.	22 to 88	52	19
Interval	8 mos. to 8 yrs. 9 mos.	3 yrs. 4 mos.	2 yrs. 1 mo.
I.Q. change . . .	-20 to $+11$	-0.3	6

Intercorrelations by the Pearson Product-Moments method:

	Malnourished	Well-nourished
Age initial vs. I.Q. rise . . .	$-.56r \pm .08P.E._r$	$-.003r \pm .106P.E._r$
I.Q. initial vs. I.Q. rise . . .	$-.199r \pm .10P.E._r$	$-.025r \pm .106P.E._r$
Interval vs. age	$-.098r \pm .10P.E._r$	$-.210r \pm .102P.E._r$
Interval vs. I.Q. rise	$-.221r \pm .102P.E._r$	$-.034r \pm .106P.E._r$
Age vs. I.Q.	$+.23r \pm .102P.E._r$	$-.007r \pm .106P.E._r$

There is a significant correlation between the age at the time of the first test and I.Q. rise. A correlation of $-.56$ is a clear indication that the younger the malnourished child when nutritional therapy is instituted, the greater the chance of improvement in mental function. Indeed, the sharp decline in average I.Q. rise for the malnourished group after the age of 4 years suggests that irreparable damage is to be expected in older children. Flexibility of I.Q. change during the first 4 years of life bespeaks of reversibility in mental development, while relative constancy in I.Q. change in older children bespeaks of irreversibility in mental development following prolonged malnutrition. The slightly positive correlation between the length of interval and I.Q. rise in the malnourished group as compared with the zero correlation of the well nourished group suggests that as long as 2 years may be necessary to bring about the average gain in I.Q. following nutritional therapy.

Summary. 1. The effect of nutritional improvement on child mentality has been determined in 182 children, 2 to 9 years of age, half institutionalized and half out-patients, for a period of 14 years.

2. The group of children malnourished at the time of the first mental test and well nourished at the time of the second test showed a rise of 10 points for the retarded and a rise of 18 points for the mentally normal, in contrast with an average zero change for the group well nourished at the time of the first test and still well nourished at the time of the second test.

TABLE 3.—I.Q. CHANGE/AGE IN MENTALLY DEFICIENT GROUP

Age	Malnourished		Well-nourished		Difference
	No. of cases	Average I.Q. change	No. of cases	Average I.Q. change	
2	11	+13.0	5	+2.4	+10.6
3	15	+14.4	7	-2.8	+17.2
4	8	+5.3	10	-1.8	+7.1
5	0	..	8	+1.6	
6	5	+1.6	9	-0.7	+2.3
7	2	+0.5	2	+1.0	-0.5

TABLE 4.—I.Q. CHANGE/INTERVAL IN MENTALLY DEFICIENT GROUP

Interval	No. of cases	Average I.Q. change	Range
6 mos. to 11 mos.	11	+5.6	-4 to +20
12 mos. to 18 mos.	12	+6.8	0 to +26
19 mos. to 25 mos.	7	+10.7	-2 to +28
26 mos. to 32 mos.	6	+11.3	0 to +23
33 mos. to 5 yrs.	5	+0.6	-10 to +9

3. The younger the malnourished child when nutritional therapy is instituted, the greater the chance of improvement in mental function since the I.Q. rise is insignificant after 4 years of age.

SALMONELLA INFECTION IN MAN

A REPORT OF 5 CASES WITH AUTOPSIES IN 2 CASES, AND A REVIEW OF THE CLINICAL ASPECTS

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In little more than half a century which has elapsed since Salmon and Smith, in 1885, first isolated the organism which they believed to be the cause of hog cholera, there has come an ever-growing awareness of the importance of salmonella infection in man. We now know that hog cholera is due to a filterable virus, and that the suipestifer organism of Salmon, a natural inhabitant of the intestinal tract of hogs, is but a secondary invader responsible for the septicemic manifestations. Nevertheless, isolation and identification of this and other organisms related to the typhoid, paratyphoid group, now all included under the generic name of *Salmonella*, have assumed increasing significance in a group of infections of varying severity frequently encountered in

clinical practice. Our knowledge has been placed on a firmer footing since the introduction of a schema of classification by White²³ and Kauffmann¹⁷ based on antigenic analyses, by means of which more than 100 types of salmonella have been identified to date. They are at present classified into 6 groups (A, B, C, D, E, F), depending on their biochemical and serologic reactions, the latter being based on agglutination tests with sera against the somatic and flagellar antigens of the organisms. Since a multiplicity of sera is required, and since some of these organisms at times show variations in antigenicity, the final identification of a strain often becomes a difficult matter, beyond the resources of the average hospital laboratory. For this reason, several Salmonella Centers have been organized where all the necessary serologic work can be performed.

Not all salmonellas have been associated with the disease in man, though it is likely that they are all potentially capable of producing such disease.⁴ Furthermore, the severity of the clinical manifestations varies with the infecting organism. For instance, of the five common salmonellas, *S. paratyphi A* and *B*, *S. typhi murium*, *S. enteritidis*, and *S. cholerae suis*, infection with *S. typhi murium* is the form most frequently encountered in the United States, and in 90% of the cases it results in a mild gastro-enteritis.^{7,20} On the other hand, by far the largest per cent of septic infections is due to *S. cholerae suis* (suipestifer). It thus becomes a matter of practical importance to identify the infecting organism as soon as possible, not solely for the epidemiologic implications, but also as an aid in prognosis and treatment. For example, if the causative organism is the *S. enteritidis* of Gärtner or the *Typhi murium* of Breslau, and the patient has recovered from the acute enteritis, we need no longer be concerned about him, provided the stool cultures have become negative; but with some of the other organisms the course may be more serious. Thus, *S. paratyphi A* produces a typhoidal course with fever and bacteremia but usually no enteritis; the *Schottmueller paratyphi B* causes enteritis, fever, sometimes visceral abscesses, and later may produce healthy carriers; while the *S. suipestifer* may occur in epidemic form when it is usually mild, or in the sporadic form when it is often severe and complicated by abscesses in various organs. During the past 2 years the following 5 cases have been observed on the medical and surgical services of the Israel Zion Hospital which exemplify the protean nature of the disease.

Case Reports. CASE 1. J. R. (116481), a 52 year old white male, was admitted to the hospital on 10/23/43, as a private patient, because of fever, weakness of the left arm and leg, and stupor of 24 hours' duration. About 2 weeks prior to the present illness he developed a sudden pain in the left side of the abdomen and fever which subsided in 2 days. On the day before admission, while at work, the patient experienced a severe chill. He was given some whiskey and sent home. A physician was called who found a temperature of 101° F., paralysis of the left arm, and some voluntary resistance to neck flexion. The following morning these signs had increased and, in addition, there was weakness of the left leg. The patient was hospitalized with an admission diagnosis of encephalitis.

The temperature was 104° F., the pulse 110, and the respirations 30. The blood pressure was 170/70. The hemoglobin was 98% (Sahli), the red cell count 4,890,000, and the white cell count 15,600 (63% stab neutrophils, 16% segmented neutrophils, 16% lymphocytes, 9% monocytes). A spinal tap yielded 5 cc. of bloody fluid under 8 mm. of mercury pressure. The blood chemistry showed 170 mg. of glucose per 100 cc., 30 mg. urea per 100 cc., an icteric index of 38, and a direct positive van den Bergh.

A neurologic consultant found the patient comatose, with moderate neck rigidity but no Kernig's sign, paralysis of the left upper and lower extremities, and a bilateral positive Babinski sign. In view of the bloody tap he felt the case was one of subarachnoid hemorrhage, although he could not rule out an inflammatory process. A second spinal tap was performed which showed clear fluid with 68 mg.% of glucose, and 5 to 6 white blood cells per c. mm. A culture of the spinal fluid was negative.

On 11/1/43, a blood culture was reported positive for bacilli of the salmonella group; these were later identified as *S. cholerae suis*. Two subsequent blood cultures were sterile. A culture of the stool was negative for salmonella, and a urine culture was not done.

Nine days after admission the patient was transferred to the medical service. At this time he presented a septic facies; he was semicomatose, irrational, and delirious. The temperature spiked to 104° F., neck rigidity was quite marked, icterus was evident, and spasticity and tenderness were present in the right upper quadrant.

The patient continued to run a septic temperature; but by 11/13/43 his sensorium had cleared somewhat, and he was more coöperative. A dry, hacking cough now became evident, and there were signs of consolidation at the right base with dulness and subcrepitant râles. On 11/17/43, a pleuritic friction rub was heard in the right axilla, and fist percussion tenderness was elicited over the liver. From here on the course continued steadily downhill, and on 11/21/43 he developed pulmonary edema and died.

The entire duration of his illness was 1 month. Treatment consisted of sulfadiazine, parenteral fluids, and supportive measures.

The final diagnoses included *S. suispestifer* septicemia, *S. suispestifer* brain abscess, cholangitis, and pneumonia.

AUTOPSY. The postmortem (4 hours after death), was limited to the chest and abdomen. The pertinent findings were as follows:

The right lung weighed 690 gm. It was adherent throughout its entire surface to the chest wall and diaphragm. The pleura was covered with a shreddy, yellowish-green, partly organized fibrinopurulent exudate extending on to the diaphragmatic surface of the lung. The consistency of the upper lobe was markedly increased. On section, the upper and part of the middle lobe showed many granite-red, granular appearing patches of consolidation. There were a few cavities, up to the size of a cherry, which were filled with frank pus. The walls of these cavities were not clearly defined and consisted of shreddy-appearing lung tissue. The lower lobe showed no evidence of consolidation but appeared poorly aerated and of bluish color. The left lung weighed 420 gm., was moderately congested on section, but appeared normal otherwise. The pleural surface of the right dome of the diaphragm was covered with a thick and largely organized fibrinopurulent exudate which was in apparent contiguity with the exudate of the diaphragmatic surface of the right lung. Corresponding to this area, an accumulation of frank, greenish-gray pus was found below the diaphragm on the right dome of the liver. The subphrenic abscess extended into the liver parenchyma proper and, on section, a fairly large part of the upper right liver lobe was involved. The liver tissue in this area was partly transformed into a necrotic débris. The rest of the liver parenchyma showed the central veins to be fairly well discernible as dark, reddish specks, and the periphery of the lobules showed a distinct yellowish tinge. The gall bladder was somewhat enlarged and moderately tense, and contained clear-green, viscid bile. The spleen was enlarged (weight 220 gm.), and of soft consistency. The capsule was dull. On section, a plum-

sized abscess cavity containing frank pus was found near the hilum. The Malpighian follicles and trabeculae were ill defined. The small and large intestine showed scattered areas of thinned mucosa and vascular congestion, but were otherwise normal.

On *microscopic examination*, the pleural surface of the lung was covered with a thick layer of partly organized fibrin throughout which were many neutrophils and round cells scattered and in focal collections. There were numerous pigment-laden macrophages. The lung parenchyma showed many areas in which the alveoli were filled with masses of partly organizing fibrin with scant cellular elements. There was an occasional large focal collection of neutrophils. Throughout were scattered macrophages containing brown pigment. In the *spleen* was a large infarct. Included in this area, and at the periphery, were seen several arteries the lumina of which were occluded by granulation tissue consisting of capillaries, fibroblasts, lymphocytes, and histiocytes. A few circumscribed abscesses were seen. The liver contained large cavities, the borders of which consisted of a layer of neutrophils with varying numbers of histiocytes, fibroblasts, and lymphocytes. The centers of the cavities contained fibrin and neutrophilic exudate. Beyond this area, many of the liver cords were replaced by fibroblasts, lymphocytes, and varying amounts of connective tissue.

Pathologic Diagnoses: *S. suispestifer* septicopyemia; confluent bronchopneumonia with abscess formation, right lung; subphrenic abscess; abscess of the liver; abscess of the spleen; acute tracheobronchitis; vascular congestion of the intestines; and atherosclerosis of the aorta, moderate. The cerebral symptoms were probably due to metastatic abscess formation in the brain.

CASE 2. T. W. (111923), a 60 year old white female, was admitted to the surgical service on 12/26/42, because of pain in the right upper quadrant and right shoulder of 28 hours' duration. This had been followed by a chill and a rise in temperature to 103° F. She had vomited once. One year before admission the patient had an attack of biliary colic; since then she suffered from epigastric distress after meals.

The temperature on admission was 103° F., the pulse 120, and the respirations 24. Physical examination revealed a cyanotic flush about the cheeks, an icteric tinge to the conjunctivae, and slight tenderness in the right upper quadrant, but no rigidity or rebound. The hemoglobin was 98% (Sahli), the red cell count 5,200,000, and the white cell count 7600 (67% neutrophils, 24% lymphocytes, 9% monocytes.) The urine contained a trace of albumin and a few leukocytes. A blood amylase determination was within normal limits.

Six days after admission the symptoms abated, and the patient was transferred to the medical service with a diagnosis of subsiding cholecystitis and possible edema of the pancreas. From a stool sent to the laboratory for routine tests and culture, a *S. newport* was recovered. A few days later a diagnostic duodenal drainage was instituted and culture of the bile revealed a *S. newport* organism.

The patient was treated with succinyl sulfathiazole until the stool cultures were reported negative. She was discharged 27 days after admission with a diagnosis of cholecystitis due to *S. newport*.

CASE 3. E. Z., a 32 year old white male, was admitted to the hospital on 3/7/43. Two days before admission he developed chills, headache, pains in the back and limbs, and fever. The following day there was a recurrence of the chills and fever associated with abdominal cramps and several loose bowel movements. On the day of admission, the patient had a 3rd chill and the temperature rose to 104° F., but by the next day it had dropped to normal.

Physical examination was entirely negative. The hemoglobin was 98% (Sahli), the red cell count 5,000,000, and the white cell count 11,200 (75% neutrophils, 2% eosinophils, 20% lymphocytes, 3% monocytes). A stool culture taken on 3/8/43 was reported positive for *S. typhi murium*. The blood culture was negative. The patient was treated with sulfaguanidine until the

stool culture was reported negative. He was discharged 9 days after admission with a diagnosis of *S. typhi murium* gastro-enteritis.

This patient had a short enteric infection due to *S. typhi murium* with fever, prostration, negative blood culture, but a positive stool culture. This organism, also known as *B. ærtrycke*, is a member of salmonella Group B. It is a natural pathogen of rodents, is pathogenic for man and other animals, and is the most frequent cause of outbreaks of salmonella food poisoning. Without the stool examination, the specific diagnosis would have been missed in this case, as it usually is in many similar cases of diarrhea.

CASE 4. M. O'H. (113126), a 53 year old white female, entered the hospital on 3/13/43, because of diarrhea of 5 days' duration. She had pneumonia when 10 years old. At 28 years of age she had an appendectomy, at 31 years a cholecystostomy, and at 34 years a cholecystectomy. Her present illness began with abdominal cramps and diarrhea following a meal of meat balls and macaroni. At the onset the bowel movements were loose and brownish with no pus or blood; the following day, however, they became foul-smelling, green, and admixed with bright red blood.

The temperature on admission was 99.6° F., the pulse 100, and the respirations 20. The blood pressure was 130/90. The patient appeared toxic and dehydrated. The pertinent physical findings were limited to the abdomen which was extremely obese. There was a large right rectus scar in the lower portion of which was an incisional hernia. There were no areas of tenderness, and no palpable masses. The liver and spleen could not be felt. Proctoscopy revealed an edematous, reddened mucosa, but no ulcerations. Pea soup stools were observed, and contents were obtained for culture.

The hemoglobin was 120% (Sahli), the red cell count 5,950,000, and the white cell count 6500 (57% stab neutrophils, 23% segmented neutrophils, 13% lymphocytes, 7% monocytes). The sedimentation rate was 53 (Westergren). A blood chemistry showed 190 mg. of glucose per 100 cc., and 58 mg. urea per 100 cc. The increased red cell count, hemoglobin, and urea were taken to be an indication of severe hemoconcentration induced by the persistent diarrhea. The stool was positive for blood, mucus, and bile, and on culture revealed a *S. newport*. A blood culture and agglutination tests, however, were negative.

The patient was placed on succinyl sulfathiazole, 1 gm. every 4 hours. The temperature varied between 99° and 100° F., and the cramps and diarrhea persisted. Ten days after admission she suddenly lapsed into a coma. The respirations were shallow, lips cyanotic, and the heart sounds unobtainable. She expired the following morning in spite of stimulation.

AUTOPSY. The postmortem (4 hours after death), was limited to the chest and abdomen. The pertinent findings were as follows:

No free fluid was present in the peritoneal cavity. The stomach and transverse colon were distended. The hepatic flexure of the colon was drawn upward to the gall bladder bed by dense adhesions. The gall bladder was not present. The spleen weighed 180 gm., its consistency was mushy, and the pulp diffuent. Malpighian follicles and trabeculae could not be distinguished. The liver weighed 1550 gm. and was flabby and friable. The capsule was smooth and glistening. The color was reddish-brown with a distinct yellowish tinge. On section, the parenchyma showed the usual architecture to be partly obliterated by a homogenous, yellowish appearance. The esophagus was normal. The stomach contained a moderate amount of brownish, semi-liquid material. The mucosal folds were somewhat atrophic, and there were streaky hemorrhages along the greater curvature and in the antrum. The small intestine was normal, except the terminal ileum, beginning at a distance of about 20 cm. from the ileocecal valve. Here the mucosa was markedly injected, dark red in spots, and showed a number of pin-point hemorrhages. There were also a number of minute ulcerations of the mucosa. The cecum displayed ulcerations behind Bauhin's valve. The rest of the mucosa of the cecum and large bowel were grossly regular. The pancreas, in general, showed the lobulated architecture to be fairly well outlined, but there was a considerable amount of

fatty and fibrous interstitial infiltration. There were also seen a number of pin-point, yellowish-white, elevated specks which had the gross appearance of fat necrosis. There was no free fluid in the thoracic cavity. The heart contained a few cc. of yellowish fluid in the pericardial sac. On serial section there were numerous pin-point sized hemorrhages through the walls of both ventricles, which in places gave the myocardium a reddish-brown color. The ostia of both coronary arteries were patent. On dissection, both coronary arteries were patent throughout, though a number of pin-point sized, elevated lipid specks were seen. The ascending aorta showed many yellowish-white, plum-to-quarter-sized elevated and partly calcified plaques. The left lung weighed 480 gm. The upper lobe was well aerated, the lower lobe congested. There was considerable anthracotic mottling. On section, a large amount of frothy fluid could be scraped off the cut lung surfaces. The color of the lung parenchyma was dark red, and there were a few grayish red, somewhat granular elevated areas grossly suggestive of consolidation. The right lung weighed 550 gm. and was similar in appearance to the left.

On microscopic examination, the heart muscle fibers showed fragmentation. Lipochrome granules were seen at the nuclear poles. In a few patchy areas, the muscle fibers were separated by cellular elements consisting of neutrophils, lymphocytes, plasma cells, and fibroblasts. These cellular elements were situated in a fibrillar network, especially around the larger vessels, but in a lesser degree could be followed into the interstitial spaces. In the lungs, many of the alveoli contained a pale staining, fluid-like material. In some areas, peribronchial collections of lymphocytes were seen. The tubular epithelium of the kidneys was swollen and desquamated in places, obliterating the lumen. There were focal collections of lymphocytes between the tubules. The mucosa of the ileum was ulcerated. However, there was only sparse lymphocytic infiltration of the wall. In the pancreas, an increase in peri- and interlobular fat and connective tissue elements were present. Between the lobules and within the meshes of the fat cells a rich cellular exudate in a fibrinous network was seen. The exudate consisted of many lymphocytes, neutrophils, and plasma cells. There was considerable fibrous replacement of the glandular elements, with fibrosis and patchy hyalinization of some of the Langerhans' islands.

Pathologic Diagnoses: Ulcerative terminal ileitis and cecitis; acute splenitis; petechial hemorrhages of the heart and liver; atherosclerosis of the aorta, moderate; and fat necrosis and fibrosis of the pancreas, moderate. The clinical picture pointed to brain involvement, although no examination of the brain was permitted.

CASE 5. E. H., a 24 year old white male, was admitted to the hospital on 4/19/43 because of abdominal cramps and diarrhea of 6 days' duration following a meal of sausage, fresh ham, and sauerkraut. The onset was associated with chill and a temperature of 102° F. The frequent bowel movements were not controlled by the usual symptomatic therapy. The cramps were colicky in character and generalized at first, but during the next 2 days they gradually localized in the left lower quadrant.

The admission temperature was 101.8° F., the pulse 70, and the respirations 20. The eyes and pharynx were congested. The heart and lungs were negative. Examination of the abdomen revealed spasm and tenderness in the left lower quadrant, and peritoneal rebound. There were similar findings in the right lower quadrant, though of lesser degree.

The urine was negative. The hemoglobin was 104% (Sahli), the red cell count 5,320,000, and the white cell count 12,000 (50% stab neutrophils, 24% segmented neutrophils, 17% lymphocytes, 9% monocytes).

Because of the duration of the complaints with diarrhea and pharyngeal congestion, a typhoid-like illness was suspected, in spite of the localizing signs in the left lower quadrant. Agglutination tests were negative for typhoid and paratyphoid. A stool specimen was positive for blood, pus, and on culture yielded a *S. paratyphi B*. The Widal was not repeated, but 2 subsequent stool cultures were positive for the Schottmueller organism.

The patient was given sulfaguanidine, 1 gm. every 4 hours, and the tem-

perature gradually returned to normal in about 4 days, the diarrhea subsided, and he became asymptomatic. He was discharged from the hospital 20 days after admission following 2 negative stool cultures. }

Discussion. *Clinical Manifestations.* Several recent analytical and statistical reviews have helped clarify the various aspects of Salmonella infection.^{4,15,20} In general, 3 clinical types may be recognized. Of these the most common is the *gastro-enteric*. It is characterized by a short incubation period (6 to 24 hours), followed by a sudden onset of gastro-enteritis, with fever, abdominal pain, vomiting, headache, and diarrhea. It may vary in severity from the mildest form of enteritis to a cholera-like syndrome terminating in death. There may be signs of localization simulating appendicitis or cholecystitis, the so-called "pseudo-surgical" syndrome.¹³ Slocum²¹ has commented on the differential diagnosis of staphylococcus and salmonella food poisoning. In the former the incubation period is shorter (2 to 4 hours), and while the symptoms are similar to those of salmonella gastro-enteritis, fever is uncommon and recovery is rapid (6 to 8 hours). The diagnosis of salmonella gastro-enteritis depends on culturing and identifying the etiologic organism, usually from the stool, but only occasionally from the urine or blood. All serologic groups of Salmonella may produce this form of infection, though *S. typhi murium* is the most frequent offender.

The second type has been designated by Bornstein⁴ as *Salmonella Fever*. Its course resembles an atypical typhoid with fever, malaise, leukopenia, and usually a slow pulse, though roseola and an enlarged spleen are often absent. The fever may be continuous or spiking with a duration of 1 to 3 weeks. As in typhoid, tracheobronchitis may occur. Localized foci do not occur in this form. The most frequent etiologic organisms in this type of infection are *S. paratyphi A* and *B*.^{6,20} However, other salmonellas may be responsible, as was true in Case 4 of our series. The diagnosis depends on isolating the organism from the blood in the earlier stages of the disease, and later in the course by specific agglutination reactions. Stool cultures are seldom positive.

The third clinical type may be called the *septicopyemic*. Its manifestations are protean, and the mortality rate is high. This form is characterized by marked invasiveness, spreading either by contiguity from an infection in the alimentary tract, or through the blood stream. There is a tendency to localize in lungs, bones, and joints; and visceral abscesses are frequent sequelæ. Salmonellas have been implicated in many localized infections including pleural and pericardial effusion,¹² pulmonary lesions,¹¹ osteomyelitis and pyarthrosis,^{9,15} endocarditis,¹⁴ meningitis,² and pelvic exudates.¹⁶ When localization occurs, leukocytosis is the rule. The symptoms consist of evidences of sepsis with other findings, depending on the points of localization. Intestinal lesions are usually absent and the causative organism is rarely recovered from the stool. The diagnosis depends on isolating the organism from the blood and/or from infected foci, and on specific agglutination reactions which are usually positive in the later stages of the disease. Members of Group C, *S. cholerae suis* in particular, are most often responsible for this type of infection.

While in general every case conforms to 1 of the 3 types,⁴ it has been pointed out by Seligmann *et al.*²⁰ that an absolute differentiation is not entirely feasible, since one may merge with another. Nevertheless, such classification is of considerable aid in furthering our understanding of the varied manifestations which may be encountered.

Epidemiology. Salmonella infection may occur in epidemic or sporadic form. While it has been possible frequently to trace the source of an epidemic, the origin of the sporadic case is more difficult to identify. The more common modes of transmission are meats of infected animals, sausage, cream puffs, ice cream, puddings, milk, and polluted water. Contaminated foods are not altered in appearance, taste, or odor, and the presence of such contamination may only be determined by bacteriologic examination. The symptom-free carrier represents a source of potential danger both to himself and to others. In a routine examination of food handlers, there were found carriers of *S. paratyphi B*, *derby*, *montevideo*, *barcilly*, *give*, *chester*, and *newport*.²⁰ The most prevalent organisms were those in Group B, while those in Group C were next. Infection may be carried from person to person by insect vectors or contaminated foods and dishes.⁵ The house fly has been implicated as a vector of *S. enteritidis*.¹⁹ Rats and mice are frequently infected with salmonella organisms, and those that recover may act as carriers, their droppings infecting cream fillings in bakeries and other stored foods to which they gain access. A contrary view has been expressed by Bartram *et al.*,³ who examined the feces of 800 domestic rats and found that these animals are not normally carriers of salmonella organisms. They feel that their importance as vectors has been overemphasized. Several European epidemics,²² and at least one epidemic in the United States,¹⁰ have been traced to infected ducks' eggs.

Pathologic Anatomy. Specific lesions have not been demonstrated. Intestinal lesions may vary from ulceration to catarrh, and sometimes, at autopsy, the intestinal findings are normal. Recently, Angrist¹ has described the pathologic findings in a case of *S. typhi marium* infection in which the gross and microscopic pictures bore a striking resemblance to typhoid fever. Otherwise, the findings are similar to other bacteremias or septicemias with splenic enlargement, petechial hemorrhages, liver necrosis, and visceral abscesses. Often the infecting organism can be cultured from these lesions.

Diagnosis. In the epidemic form no difficulty should be encountered. The sporadic case necessitates a constant awareness of the possibility of a Salmonella infection being present. All acute diarrheas should have a bacteriologic examination of the stool, while every case of prolonged fever of undetermined origin should have a culture of the blood, urine, and feces. In addition, when specific agglutination tests are being done, those for salmonellas should be included.

Prognosis. As in many bacterial infections, this depends largely on the condition of the patient, and the type, virulence, and dose of the infecting organism. Fatalities are common in infants and debilitated adults, or in those suffering from chronic illness. There were 5 deaths in 51 cases of salmonella fever, and 18 deaths among 49

cases of the septic type collected by Bornstein.⁶ Members of Group C, especially *S. cholerae suis*, account for most of the deaths, because of their invasive tendencies. Seligmann *et al.*²⁰ have analyzed 1000 cases of salmonella infection of all types. Positive blood cultures were found in almost 60% of those due to *S. cholerae suis*, while *S. paratyphi B* was next with 22%. Both of our cases that came to autopsy were due to members of Group C; Case 1 being due to *S. cholerae suis*, while in Case 4 a *S. newport* was the infecting organism. The gastro-enteric form is usually mild, most cases recovering in 3 to 5 days. An occasional fatality occurs.

Treatment. For the present, this must remain largely symptomatic. Abscesses may be drained, and foci removed surgically. Serum therapy has been attempted, and at least 1 cure with rabbit Group C antiserum has been reported.¹⁸ Vaccines may be used both prophylactically and in chronic infections. Sulfaguanidine has been found to be bacteriostatic *in vitro* for *S. cholerae suis* and *S. paratyphi A*, but is without effect on other salmonellas.⁸

Summary and Conclusions. 1. Salmonella infections are more common than is generally recognized.

2. They may be mild and localized, or severe and invasive.

3. Most cases recover promptly; some are fatal in a few days; while others remain ill for a much longer time in a typhoidal state, with or without the development of metastatic abscesses.

4. The diagnosis depends on recovering the organism from the blood, urine, or feces; later in the course specific agglutination reactions may be positive.

5. The symptom-free carrier represents a source of potential danger to himself and the community.

6. Five cases have been presented, illustrating some of the varied manifestations of salmonella infection in man.

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LESIONS IN RATS FED SULFAGUANIDINE IN PURIFIED DIETS THE EFFECTS OF LIVER OR "FOLIC ACID" CONCENTRATE- BIOTIN THERAPIES

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PROFOUND disturbances, similar in many respects to those observed in vitamin deficiency syndromes, are produced by the administration of sulfaguanidine or sulfasuxidine to growing rats receiving a highly purified diet.^{4-7,9-11,17,21,23,24,25,28,31,33,34,36} Many of these toxic manifestations can be prevented or cured by various dietary factors.^{4-7,9-11,17,21,23,24,25,28,31,33,34,36} Hyperplasia of the thyroid gland produced by these drugs has been cured by the administration of thyroid powder or thyroxin.^{3,22} However, the effect of dietary factors upon certain other lesions has not been reported.

There is evidence to indicate that some toxic effects are caused by the ability of the sulfonamides to inhibit synthesis of essential factors by the intestinal bacteria. It is recognized, however, that these drugs may also exert a general, systemic effect by interfering with certain vital enzyme systems within the tissues.

The present report is concerned with the lesions observed during the course of sulfaguanidine administration and their evolution or involution under therapy. A more detailed report of the nutritional aspects of this subject will be given in a subsequent paper.

Methods. Weanling, albino rats from the Sprague-Dawley colony were employed. The basal ration had the following composition: sucrose 76, Labco casein 18, salts¹⁸ 4, corn oil 2 and 1 mg. of 2-methyl-1,4-naphthoquinone. In addition, all animals received B vitamins daily in supplement dishes in the following doses: thiamine 30 γ , pyridoxine 30 γ , riboflavin 30 γ , calcium pantothenate 100 γ , and choline chloride 10 mg. Two drops of haliver oil containing 1.3 mg. of d,l- α -tocopherol acetate were given weekly to each rat.

One series of 60 rats was given the basal ration to which 1% of sulfaguanidine had been added, while another series of 48 rats received 0.5% of the drug in the basal diet. This is roughly equivalent to a human dosage of 150 and 75 gm. daily. A group of 25 rats received the basal diet alone. Five animals of the latter group were given, in addition, whole liver substance (Wilson's), comprising 10% of the ration, at the expense of the sucrose. A final group of 5 rats received 1% of sulfaguanidine with 10% of whole liver in the basal diet from the onset of the experiment.

The substances tested for their therapeutic value in the leukopenia which results from the sulfaguanidine administration have been described in a previous publication.⁴ With the exception of whole liver and a "folic acid"

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concentrate, the test substances were ineffective. For the purposes of this report the animals are divided into three groups:

- A. Seventy rats given sulfaguanidine and ineffective or no treatment.
- B. Forty-three rats given sulfaguanidine and liver or "folic acid" concentrate (prepared from liver) plus biotin. The 5 animals which received liver and sulfaguanidine in the basal diet from the onset of the experiment are included here.
- C. Twenty-five rats (control) on basal diet.

Rats of Series A and B were maintained on the experiment for 9 weeks before therapy was instituted. Periodic blood studies were made before and after the institution of therapy. At this time laparotomies were performed under ether anesthesia on 21 rats from the 0.5% sulfaguanidine series for the purpose of observing the gross appearance of the liver. Tissue for biopsy was removed from the liver of 6 rats, and they, with 2 others, were immediately given "folic acid" concentrate and biotin.

Seventeen survivors of 4 months of 1% sulfaguanidine administration, all but 2 of which had received liver or "folic acid" concentrate plus biotin, were given thyroxin in doses of 1 γ per gm. of body weight subcutaneously for periods varying from 2 to 6 weeks.

All survivors were sacrificed at the end of the experiment, after more than 5 months of observation. Autopsies were performed on all animals and sections were taken from the heart, lungs, liver, spleen, kidneys, sternum, adrenals, thyroid gland and skeletal muscle.

Results. GENERAL OBSERVATIONS. Animals fed sulfaguanidine showed retardation and finally cessation of growth, a debilitated general appearance, and a severe leukopenia. These adverse effects of sulfaguanidine administration are similar to those previously reported. The development of a state of shock in many of the untreated rats was of particular interest. This was characterized by lowered body temperature, general apathy, and flaccidity of the tissues. In these rats great difficulty was experienced in obtaining sufficient blood from the tail veins for a white cell count. What blood could be obtained tended to clot almost immediately. The above symptoms could be prevented or cured in a large majority of the animals by the administration of liver or of a combination of "folic acid" concentrate and biotin.

MORTALITY RATE. Within 3 months 87% of the rats of group A, but only 13% of the rats of group B died. All of the control animals (group C) survived.

GROSS AUTOPSY FINDINGS. More than one-half of the animals of group A showed *liver* lesions. These consisted of pin-head size and larger, opaque, white spots, beneath the capsule and irregularly scattered over the cut surface. Many livers, particularly those on the smaller drug dosage, showed larger areas of necrosis which involved from 10 to 50% or more of the liver substance. Indeed, in several animals no normal liver tissue could be seen. These livers were greatly enlarged, almost pure white in color, devoid of normal markings, and exceedingly friable. They gave the appearance of massive infarction. Only 2 of the rats of group B showed liver lesions. These consisted of pin-head sized, chalky-white foci. The distribution of the gross liver lesions is given in Table 1.

The *spleens* also showed focal necroses grossly (Table 2). The necrotic foci were 2 to 4 mm. in diameter, a deeper yellow than those

TABLE 1.—THE EFFECT OF THERAPY ON THE DISTRIBUTION OF GROSS AND MICROSCOPIC LIVER LESIONS PRODUCED BY THE PROLONGED ADMINISTRATION OF SULFAGUANIDINE

Amount of sulfaguanidine in diet	Gross lesions						No lesion			Active* lesions			Healing lesions													
	A			B			C			A			B			C										
1.0%	19/32 60%	2/31 6%	0/10 0%	3/31 10%	23/31 74%	10/10 100%	26/31 84%	5/31 16%	0/10 0%	3/31 10%	4/31 13%	0/10 0%	18/38 47%	0/8 0%	0/15 0%	7/36 19%	7/8 88%	15/15 100%	27/36 75%	1/8 13%	0/15 0%	13/36 36%	5/39 13%	0/25 0%
0.5%	37/70 53%	2/39 5%	0/25 0%	10/67 15%	30/39 77%	25/25 100%	53/67 79%	6/39 15%	0/25 0%	16/67 24%	5/39 13%	0/25 0%	Total											

* Degenerative or necrotizing lesions with little or no reaction.
A—Rats given ineffective or no treatment.
B—Rats given liver or "folic acid" concentrate plus biotin.
C—Control rats on basal diet without sulfaguanidine.
The numerator of the fractions indicates the number of rats in which the finding was noted.
The denominator of the fractions indicates the total number of rats in the group.

TABLE 2.—THE DISTRIBUTION OF LESIONS IN SPLEEN, LUNG AND HEART PRODUCED BY THE PROLONGED ADMINISTRATION OF SULFAGUANIDINE

Amount of sulfaguanidine in diet	Microscopic lesions																	
	Gross lesions			Necrosis or infarction with or without bacterial invasion						Healing lesions			Microscopic lesions					
	Necrosis or infarction			A			B			C			Bacterial emboli, pneu- monia, or molecular cell mobilization			Focal necrosis or cellular infiltration		
	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C			
1.0%	11/32 34%	1/31 3%	0/10 0%	17/26 65%	2/28 7%	0/10 0%	7/26 27%	2/28 7%	0/10 0%	21/31 68%	17/30 57%	2/9 22%	1/31 3%	5/31 16%	0/10 0%			
0.5%	3/38 8%	0/8 0%	0/15 0%	7/32 22%	0/8 0%	0/12 0%	0/32 0%	0/8 0%	0/12 0%	19/36 53%	2/8 25%	2/12 17%	2/35 6%	0/8 0%	0/12 0%			
Total	15/70 21%	1/39 3%	0/25 0%	24/58 41%	2/36 6%	0/22 0%	7/58 12%	2/36 6%	0/22 0%	40/67 60%	19/38 50%	4/21 19%	3/66 5%	5/39 13%	0/22 2%			

Letters and fractions as in Table 1.

in the liver and elevated above the surface. They were irregularly distributed. Occasionally more than one-half or even the entire spleen was necrotic. This was suggestive of infarction.

Urinary tract lesions were encountered in the 1% sulfaguanidine series only (Table 3). All of these lesions were caused by urinary obstruction due to stones. The *kidneys* were usually enlarged, pale, soft and edematous. The pelves were greatly dilated. The *ureters* were also frequently dilated, and impaction of stones at the ureteral orifices of the bladder were not uncommon. Stones were also found in the renal pelves, occasionally in the bladder, and even in the urethra. The stones varied in size from sandlike granules to irregular, yellow to brown, hard masses up to 3 mm. in diameter. Several of these were washed free of adherent soluble material and then analyzed qualitatively for sulfonamides. They were found to contain large amounts of free and acetylated sulfonamide with the latter predominating. In a few instances the kidneys were dark brown in color and the surfaces were granular and irregularly pitted. This scarring was interpreted as resulting from a pyelonephritis.

Many of the *lungs* showed pin-head sized, subpleural, chalk-colored foci which were not elevated above the surface. They were seen occasionally in control animals, but were encountered much more frequently in the experimental rats.

Enlargement of the *thyroid* gland to more than twice the normal size was noted in many animals. This finding was as frequent in the treated as in the untreated rats, but was more common in the 1% group than in the group on 0.5% drug.

In some rats the *intestines* were distended with fluid and gas and suggested the picture of paralytic ileus.

No other significant findings were noted grossly. It is worth emphasizing that none of the control rats showed any spontaneous lesions, so that those described may safely be ascribed to the results of treatment received.

MICROSCOPIC FINDINGS. Because of the complicated and varied character of the microscopic changes, they will be described first and their distribution noted subsequently.

Liver. The microscopic alterations in the liver include cloudy swelling, hydropic degeneration, various types of necroses, fatty degeneration, hepatitis, bacterial invasion, and varying degrees of repair.

Albuminous degeneration: This may be slight in degree, but in most instances it is severe. However, even when severe, it is commonly the least striking lesion. The swelling of the hepatic cells is at times so great that the sinusoids are all but obliterated. In a number of rats, scattered hepatic cells contain coarse to large, angulated, basophilic cytoplasmic granules. Such cells are conspicuous because of their purple color in the hematoxylin-eosin preparations. The nuclei of the hepatic cells may be normal, but many are enlarged, the chromatin is scanty, and the color is pale. Fragmentation of the liver cords and dissociation of the liver cells is occasionally associated with this, as well as with the more serious alterations in hepatic architecture.

TABLE 3.—THE DISTRIBUTION OF GROSS AND MICROSCOPIC RENAL LESIONS PRODUCED BY THE PROLONGED ADMINISTRATION OF SULFAGUANIDINE

Amount sulfaguanidine in diet	Gross lesions											
	Urolithiasis, with hydronephrosis or hydroneureters						Chronic pyelonephritis					
	A	B	C	A	B	C	A	B	C	A	B	C
	6/32 19%	5/31 16%	0/10 0%	2/32 6%	2/31 6%	0/10 0%	1/31 3%	5/31 16%	0/10 0%	7/31 23%	0/31 0%	0/10 0%
0.5%	0/38 0%	0/8 0%	0/15 0%	0/38 0%	0/8 0%	0/15 0%	0/37 0%	0/8 0%	0/15 0%	3/37 8%	0/8 0%	0/15 0%
Total	6/70 9%	5/39 13%	0/25 0%	2/70 3%	2/39 5%	0/25 0%	1/68 2%	5/39 13%	0/25 0%	10/68 15%	0/39 0%	0/25 0%

Letters and fractions as in Table 1.

TABLE 4.—THE EFFECT OF THERAPY ON THE ACTIVITY OF BONE MARROW AND THYROID GLAND IN RATS GIVEN PROLONGED SULFAGUANIDINE TREATMENT

Amount of sulfaguanidine in diet	Bone marrow activity											
	Hyperplastic						Hypoplastic					
	A	B	C	A	B	C	A	B	C	A	B	C
	6/28 21%	24/26 92%	22/28 79%	2/26 8%	12/26 46%	5/25 20%	14/26 54%	20/25 80%
0.5%	9/27 33%	8/8 100%	15/15 100%	18/27 67%	0/8 0%	0/15 0%	28/28 100%	5/8 63%	0/28 0%	3/8 38%
Total	15/55 27%	32/34 94%	40/55 73%	2/34 6%	40/51 74%	10/33 34%	11/13 85%	14/54 26%	23/33 70%	2/13 15%

* Animals which received thyroxin are excluded from the tabulation.

Letters and fractions as in Table 1.

The Kupffer cells are frequently greatly swollen. The sinusoidal lining is often detached, and the space between the liver cells and the sinusoidal lining contains acidophilic granular material. The sinusoidal lumens may contain little or no blood, but considerable granular material.

Hydropic degeneration: The most striking and severe alteration in architecture is produced by an enormous swelling of the hepatic cells. This swelling has frequently progressed to the point of cell-wall rupture. The cytoplasm is colorless and clear except for a few remnants of delicate reticulum radiating from a centrally situated, round nucleus. The nuclei are generally smaller than those of normal hepatic cells and stain more deeply. The cytoplasm does not stain with any of the more common water-soluble dyes. Negative results are also obtained with fat-soluble dyes (frozen sections) including Sudan IV, Nile blue sulfate, and those used in the Lorrain Smith-Dietrich stain. Celloidin sections stained by the Best-carmin technique* show no glycogen in the swollen clear cells. Severe glycogen depletion is apparent throughout the sections. These large cells may be found scattered and single, but more commonly they are grouped in clusters of 6 to 20 cells. They may be found in central, peripheral or mid-zonal positions. In some animals the hydropic degeneration is extensive, involving many contiguous lobules, and may be so severe that the liver tissue is scarcely recognizable (Fig. 1). Occasionally a few of the degenerated cells contain coarse, angulated, basophilic cytoplasmic granules similar to those seen in cells which have undergone cloudy swelling. Other cells in the same section may show extensive vacuolization with slight to moderate clearing of the cytoplasm. These represent a less severe degree of hydropic degeneration. Generally, however, cells adjacent to the swollen clear cells show a dense, acidophilic cytoplasm.

Necroses: Various types of necroses are encountered. The necrotic foci are also variable in distribution, shape and size. When the necrosis is central, the hepatic cells immediately adjacent to the vein are not involved. The necrotic areas are usually one-third to two-thirds the size of a lobule. Some are elongated and interconnect with one another (Fig. 2). The necrosis is usually coagulative in type, but may be hyaline. With the former, the outlines of hepatic cords and sinusoids may be obliterated, while with the latter, not only are the cords and sinusoids intact, but the cell outlines may also be discernible. The cells which have undergone hyaline necrosis are shrunken; the nuclei are absent; the cytoplasm is dense, deeply acidophilic and homogeneous. The sinusoidal spaces are dilated and empty. With very few exceptions the necrotic regions and their periphery show no cellular infiltration, but adjacent viable liver cells exhibit varying degrees of degeneration. There is usually a severe proliferation and swelling of Kupffer cells, many of which are desquamated and degenerated.

* Only a few animals were selected for glycogen studies. Care was taken to allow no more than 1 minute between the death of the animal and fixation of a thin slice of liver in absolute alcohol.

Occasionally a small necrotic focus is found immediately subjacent to the intima of a portal vein (Fig. 3). The overlying endothelial cells are swollen and desquamated, while the lumen contains a recent fibrin thrombus.

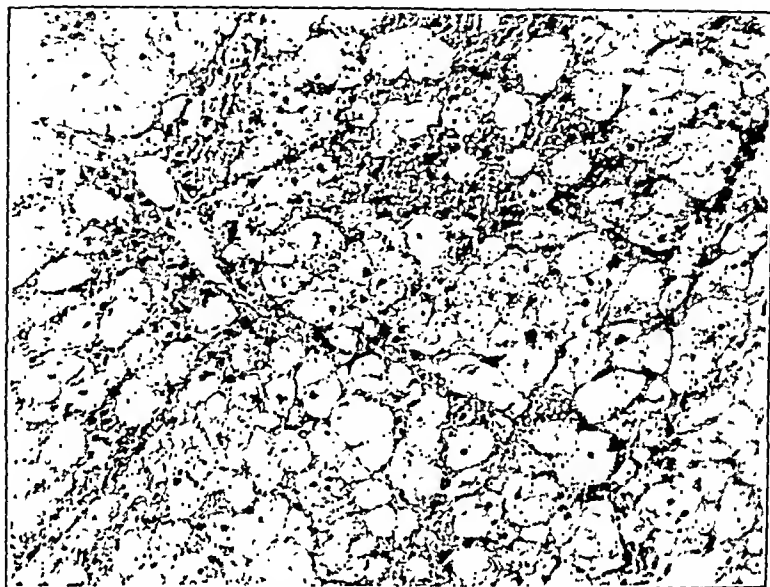


FIG. 1.—Hydropic degeneration of liver. Many large clusters of swollen cells with clear cytoplasm involve several contiguous lobules. Cells adjacent to the clear cells are essentially normal. Rat on 1% sulfaguanidine, untreated.



FIG. 2.—Necrosis of liver, coagulative in type. Interconnecting bands of necrosis isolate and surround portions of lobules. There is no cellular reaction to the necrosis. Small focal hemorrhages are present. Rat on 0.5% sulfaguanidine, untreated.

The most extensive necroses are those secondary to infarction and this may involve a part of a lobe or, at times, most of the liver. Slight to severe hemorrhage accompanies the infarctions. The periphery of

the infarcted areas shows no marginal zone of leukocytic infiltration. There is no cellular reaction other than a moderate intensification of the proliferation and swelling of the Kupffer cells seen elsewhere. Many sinusoids and hepatic, as well as portal, veins in the infarcted zones are occluded by recent fibrin thrombi.

The least striking of the necroses involve isolated cells or clusters of cells. These represent the end-stage of progressive degenerative processes. The necrotic cells are in various stages of disintegration and they contribute considerably to the cellular debris present in the areas of degeneration.

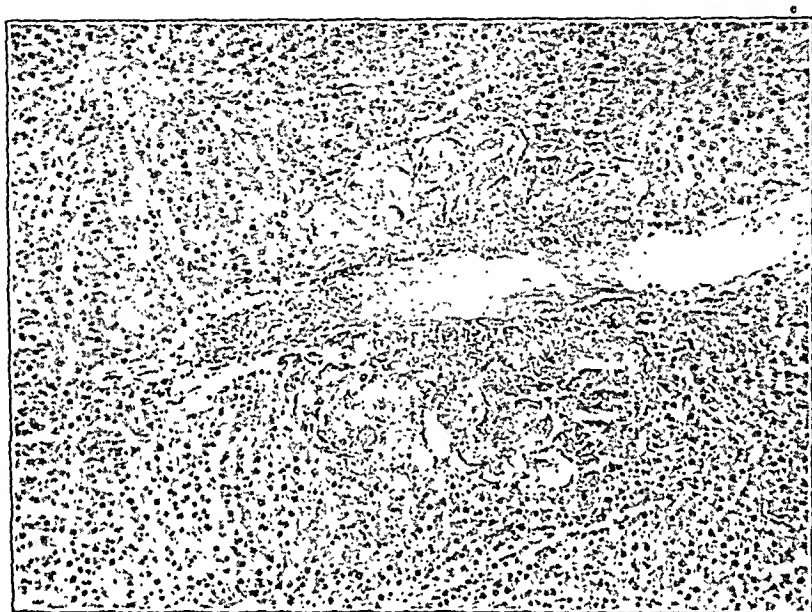


FIG. 3.—Focal necrosis about a vein. A delicate fibrin thrombus occludes the vein in the region of necrosis which also involves the wall of the vein. There is no cellular reaction to the necrosis. Rat on 1% sulfaguanidine, untreated.

Fatty degeneration: Frozen sections stained with Sudan IV, Nile blue sulfate, and by the Lorrain Smith-Dietrich method exhibit droplets of neutral fat and other lipoids in the liver cells near regions of necrosis and hydropic degeneration. The amount of neutral fat and other lipoids in the cells is variable and often great. The distribution of the involved cells is irregular. In some regions the central zones show large amounts of neutral fat only; while in other sections there is little or no neutral fat in the central zones, but the mid-zonal or peripheral zones show both neutral fat and other lipoids in small to moderate amounts. Very little lipoid is found in livers which show minimal or no involvement.

Hepatitis: The only general reaction to the various degenerative and necrotizing processes is a proliferation of the Kupffer cells which are swollen, at times to the size of hepatic cells, and frequently desquamated. Some of these cells contain dark, almost black pigment and some contain green pigment. However, no iron is demonstrable by

the Prussian-blue reaction and most of the Kupffer cells contain no pigment, although phagocytized cell débris and vacuoles are seen occasionally within the cytoplasm. In and near the necrotic zones the Kupffer cells are also necrotic and their débris constitutes a large component of the sinusoidal content.

Bacterial invasion: Many, but by no means all, foci of coagulation necrosis contain large, centrally situated masses of bacteria. These are usually gram-positive cocci or bacilli, but in some instances gram-negative bacilli are also present. The tissues adjoining the necrotic area are usually free of bacteria. Occasionally bacterial masses are found within the lumen of veins occluded by recent fibrin thrombi. Neither the foci invaded by bacteria nor the adjoining tissues show

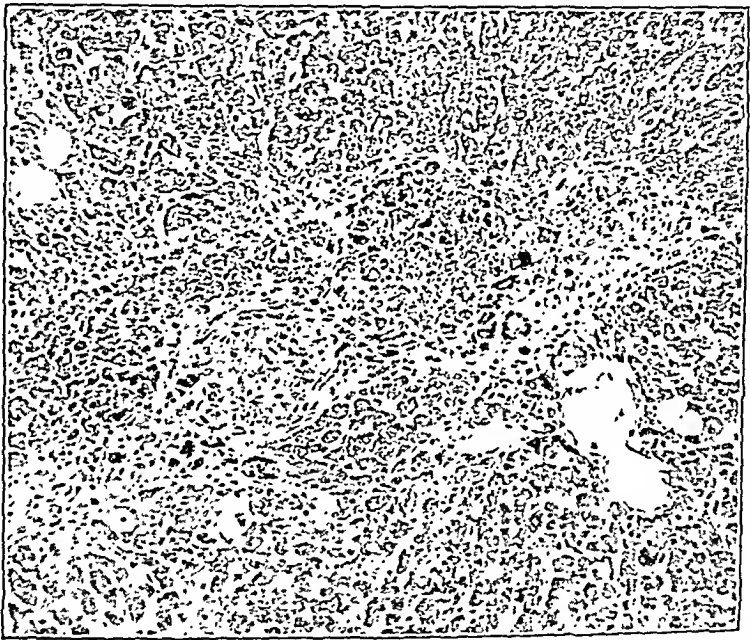


FIG. 4.—Scar in liver. There are numerous proliferated bile ducts and giant cells in the scar tissue, along with pigment-laden phagocytes, endothelial cells, and some remnants of cellular débris. Rat on 0.5% sulfaguanidine, untreated.

any reaction to the presence of the microörganisms. No bacteria are seen in areas of hyaline necrosis or in the vicinity of necroses which involve single cells or small cell groups. Infarcted zones are only occasionally involved by bacteria. Bacteria are found only in animals which died spontaneously.

Repair: Evidence of repair is found in relatively few animals. There are four indications of this process. The most obvious indication is the presence of large scars (Fig. 4). These scars are composed of loosely arranged or fairly dense connective tissue, moderately rich in fibroblasts, and relatively avascular. Large monocyctic phagocytes containing yellow pigment or with vacuolated cytoplasm are loosely scattered throughout the connective tissue. Many scars also contain lymphocytes in small foci and also more widely and more sparsely

distributed. Many of the scars also contain proliferated bile ducts and sometimes groups of liver cells. Occasionally a small hepatic lobule is surrounded by scar tissue.

A second indication of repair is the presence of multinucleated giant cells (Fig. 5). These giant cells contain 3 to 8 nuclei. The origin of these cells appears to be mostly from Kupffer cells, but also from bile duct epithelium, and occasionally from liver cells (Fig. 6). The appearance of the nuclei varies accordingly. Those derived from the Kupffer cells are darker and smaller. The cytoplasm is commonly pale, but occasionally it is deeply acidophilic. The giant cells are frequently numerous, but are found in only a few of the animals. Some are seen in relation to scar tissue, but more often they are present in various parts of a hepatic lobule which shows no scarring.

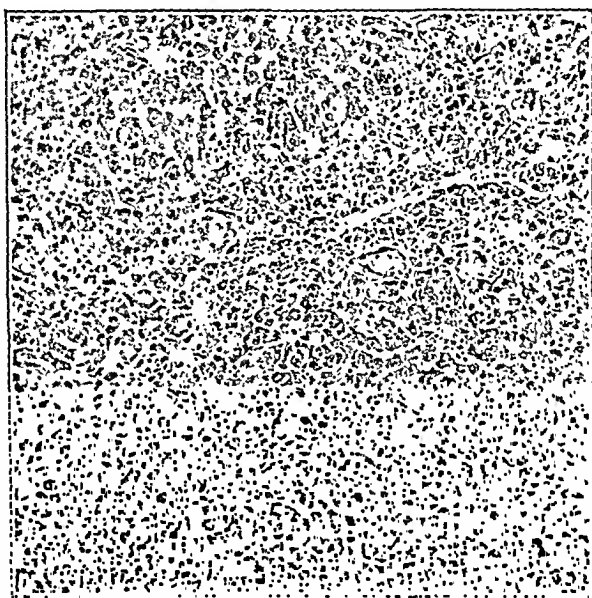


FIG. 5.—Repair of liver lesion, the formation of numerous giant cells. These appear to be formed by endothelial cells. There is much fragmentation of the liver cords and a small amount of cellular debris is present. Rat on 0.5% sulfaguanidine, untreated.

Bile duct proliferation is found in a small number of rats. Although pronounced in scar tissue, this proliferation is also seen in the peripheral zones where no scar tissue is present.

A fourth but less obvious indication of repair is an alteration of architecture without scar tissue production. The lobules are of various sizes, irregular in outline, and their anatomic limits are ill-defined. In these sections there are many isolated hepatic cells which are conspicuous by their deeply acidophilic cytoplasm. Many hepatic cells are binucleated, and multinucleated syncytial liver cell masses are encountered (Fig. 6). The nuclei of other cells may vary considerably in size and chromatin content. Some nuclei are very large, hyperchromatic, and show a very coarse chromatin network. Occasional nuclear monstrosities are noted (Fig. 6).

No bacteria are found in the regions which show evidence of healing. In 1 animal a chronic purulent perihepatitis is seen.

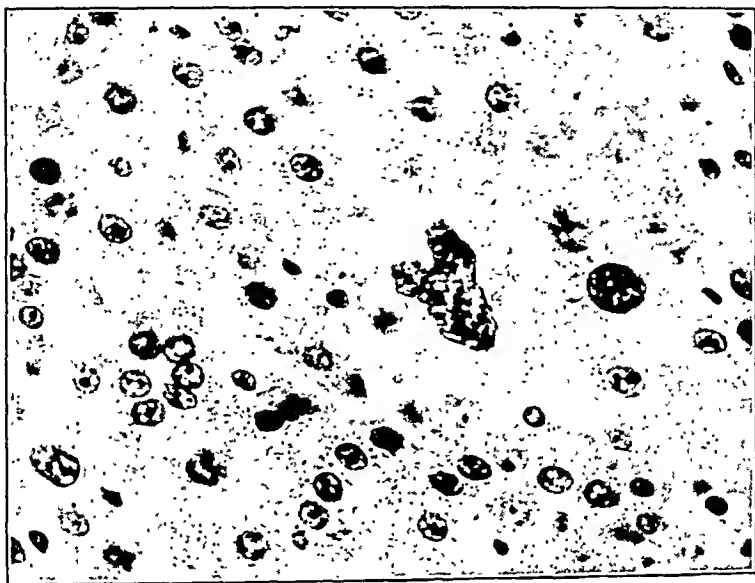


FIG. 6.—Repair of liver lesion, the formation of syneytia by cells of the hepatic cords. Note giant cell with 9 nuclei; the nuclei vary in size and staining-intensity. There is a nuclear monstrosity. Rat on 1% sulfaguanidine treated with liver.



FIG. 7.—Repair of splenic lesions. There are irregular, collagenous foci which contain small masses of deeply basophilic amorphous material (calcific?). The collagenous foci are infiltrated scantily by endothelial cells, some of which possess foamy cytoplasm. Rat on 1% sulfaguanidine, treated with "folic acid" concentrate plus biotin.

Liver sections of some rats which received liver or "folic acid" concentrate therapy show minute hematopoietic foci and occasional nucleated red blood cells in the sinusoids.

Spleen. Rounded foci of coagulation necrosis, with and without bacterial masses similar to those observed in the livers, are present

in the spleen of many rats. As many as 4 to 6 foci are seen in some sections. They vary in size from one-third to twice the size of a follicle and may involve the periphery of splenic corpuscles or the pulp. Thrombosis of splenic vessels is frequent. This thrombosis is of recent character and no reaction in the vessel wall is seen even when bacteria are present in the lumen. No exudation accompanies the necrosis of splenic tissue.

Many spleens show small or extensive infarctions, sometimes involving as much as three-fourths of the spleen. The infarcted zones show no marginal leukocytic infiltration. Profuse proliferation of endothelial cells is frequent and is associated with a corresponding paucity of lymphocytes and an almost complete absence of splenic corpuscles. The endothelial cells frequently contain a large amount of hemosiderin. Some spleens show a progression of this process with the diffuse laying down of collagen fibers, obliterating the normal sinusoidal architecture. These alterations may involve large portions of a spleen, but in other regions of the same section little to moderate alteration may be present.

There are a number of rats in which the necrotic foci are partially or completely replaced by dense scar tissue. In this scar tissue there are deposits of deeply basophilic amorphous material suggestive of calcium salts; large, lipophage-like cells, monocytes, and occasional multinucleated giant cells are also present (Fig. 7).

In the same animal which shows purulent perihepatitis a similar perisplenitis is noted.

Many animals which received liver or "folic acid" concentrate plus biotin therapy show pronounced leukopoietic activity in the splenic pulp. This is absent in animals not so treated.

Sternal Bone Marrow. The histologic picture of the sternal marrow varies from almost complete aplasia to intense hyperplasia. In the severely hypoplastic marrow cytoplasmic blobs without nuclei are noted, as well as many large, pale, endothelial-like cells. The latter are frequently degenerated and the nuclei pyknotic. Megakaryocytes in these sections are greatly reduced in number and show similar degenerative changes.

Heart. Lesions in the heart are infrequent. They are isolated, minute, and usually situated subepicardially in the left ventricle. Several foci of necrosis involving one or two muscle fibers are encountered. Occasionally neutrophilic leukocytic infiltration of two or three myocardial fibers and the associated stroma is noted. Similarly small foci of fibroblastic proliferation are present in several animals. In a few rats several myocardial capillaries are found occluded by bacterial masses. The adjoining tissues show no reaction to the presence of the bacteria.

Lungs. Subpleural collections of large, almost colorless cells with very small, round, central nuclei are frequent. These cells often completely fill the alveolar spaces and resemble alveolar phagocytes (Fig. 8). Occasionally these cells are also seen about bronchi and vessels.

Many animals exhibit bacterial masses in alveoli and the lumens of large blood-vessels and alveolar capillaries. As a rule, the pulmonary tissue shows no reaction to the presence of the bacteria. In some lungs alveoli adjacent to the bacteria contain edema fluid and occasionally fibrin. In one instance the reaction consists of severe swelling, proliferation and desquamation of alveolar cells. Leukocytes are generally absent. Vessels near the bacterial masses are often occluded by recent fibrin thrombi. The walls of vessels containing bacterial emboli show no reaction. In one control rat an interstitial pneumonitis is present.



FIG. 8.—Subpleural collections of large, swollen endothelial cells which completely fill some of the alveoli. Rat on 1% sulfaguanidine treated with "folie acid" concentrate plus biotin.

Kidneys. Cloudy swelling of tubular epithelium is present in many animals, but it is severe in only a few, where it is associated with casts and débris in the lumens. Deposits of structureless, deeply basophilic material are frequent in the medulla, but may be seen occasionally in the cortex as well. These deposits, which resemble calcific material, lie between the tubules and do not involve the latter. They appear to fill spaces lined, at least partially, by delicate endothelial-like cells (lymphatic spaces?). There is no inflammatory reaction adjacent to these deposits. In some rats there are subepithelial deposits and encrustations at the pyramidal tips, and papillary projections bulging with this calcific (?) material may project from the pyramids into the

pelvis. Some of these papillæ have become detached and lie as foreign bodies in the urinary pelvis. All animals with the latter finding were afflicted with gross uroliths.

Some of the rats which exhibit bacteria in the liver or spleen also show bacterial emboli in the kidneys. An occasional glomerulus is partially or completely obliterated by the bacterial masses. Inflammatory reactions are absent in all but one instance. In one rat, proliferation of glomerular epithelium and endothelium is present and early glomerular adhesions are demonstrable.

In a number of rats, varying degrees of pyelonephritis are encountered. Some of these inflammations are focal in distribution, while others involve the entire kidney diffusely.

Indications of past urinary obstruction are seen in moderate to severe dilatation of the collecting tubules, particularly at the tips of the pyramids, and occasionally also of the convoluted tubules. This finding is more frequent with the larger sulfaguanidine dosage. Occasionally a delicate scaffolding of fibrils outlining angular spaces within dilated tubules suggests the site of crystal deposits.

Adrenal Gland. Although this organ was not sectioned in all rats, generally no significant lesion is found. In several instances isolated, minute, cortical, focal necroses and small hemorrhages are noted.

Thyroid Gland. Hyperplasia of the thyroid is frequent. The degree of hyperplasia varies considerably and is often of severe degree. The hyperplastic glands are composed of relatively small acini lined by pale, exceedingly tall epithelium with empty, and in some instances, virtually non-existent lumens.

Skeletal Muscles and Vessels. No lesion of skeletal muscles or of vessels is noted.

Distribution of Microscopic Findings. For the purpose of a better perspective, the degenerative and necrotizing lesions of the liver have been grouped together and tabulated under "active lesions" in Table 1. All lesions of the liver suggestive of repair have likewise been grouped together in this table under the heading of "healing lesions."

The distribution of significant microscopic lesions in the spleen, lungs and heart is given in Table 2. Microscopic renal lesions are classified and tabulated in Table 3.

The sections of bone marrow are graded from 0 to 4+ according to the activity exhibited. On an arbitrary basis, the bone marrow with 3+ or 4+ activity is classified as hyperplastic, while bone marrow with 2+ or less activity is classified as hypoplastic in Table 4.

The sections of thyroid gland are similarly graded in this table according to the degree of hyperplasia, from 0 to 4+. Because the thyroid glands of many control rats show 1+ hyperplasia, this is taken as the upper limit of activity of the resting state. Activity above this grade is classified as "hyperplastic." The thyroid glands of all animals which received thyroxin, with the exception of one, are in a resting state microscopically.

Observations in Laparotomized Animals. Grossly only 2 of the livers observed at operation showed foci of necrosis. The remaining 19

appeared normal or exhibited varying degrees of pallor. Hydropic and other degenerative changes were noted microscopically in 5 liver sections taken from 6 of the 8 animals which subsequently received "folic acid" concentrate plus biotin. Foci of necrosis were present in 2 of the 5.

One animal with a normal liver at laparotomy died within 24 hours after the operation and then had a completely infarcted liver. This liver was enlarged, pale, almost white, soft and friable. The cut surface was almost completely devoid of structural markings. This infarction could not be ascribed to operative vascular damage.

The 2 animals showing foci of liver necrosis at operation and 4 of the others died within 3 days. Five more rats succumbed within 1 month following laparotomy; only 1 untreated rat and all 8 treated with "folic acid" concentrate plus biotin survived to the end of the experiment, approximately 3 months after operation. On microscopic section, liver lesions were observed in 11 of the 13 untreated animals, but in only 1 of the 8 animals receiving "folic acid" concentrate plus biotin. The liver of this treated animal showed healing as well as active lesions.

Relation of Hepatic Lesions and Bone Marrow Activity. A close parallelism exists between the pathologic alterations of the liver and the activity of the bone marrow. In 76% of the animals whose liver shows necrosis or hydropic degeneration, or both, the bone marrow is hypoplastic (0 to 2+). On the other hand, in 77% of rats with normal liver the marrow is hyperplastic (3+ to 4+). Eighty-five % of the rats with hypoplastic marrow (0 to 2+) show the above hepatic lesions, whereas 84% of the rats with maximally active marrow show no hepatic lesion.

Discussion. Clinical^{8,13,15,26,27,35} and experimental^{1,2,9,12,19,20,29} reports of hepatic lesions produced by sulfonamides indicate that they are largely degenerative and focally necrotic. There is good basis for the belief that any one of the sulfonamides in common clinical use may be capable of producing similar disturbances. Thus, Menten and Andersch²⁶ have recently described degenerative and necrotizing lesions of the liver in children given various sulfonamides and they have also found disturbance in function.

In the present experiment, similar results were obtained and the sole indication of inflammatory reaction in the liver or spleen, with few exceptions, is the proliferation and swelling of endothelial cells. The absence of exudative reactions was a dominant feature and this may be related to the associated leukopenia.

There are indications that the larger areas of necrosis are infarctions. The association of the necrotic foci with vascular thrombosis supports this assumption. The explanation for the thrombotic vascular occlusions may be sought in the hemoconcentration incident to shock, the attendant increased blood viscosity, the diminished blood flow, and the consequent increased tendency of the blood to clot.

It appears from the present experimental results that the hepatic changes exclusive of infarction are to a large extent reversible and

reparable. The administration of liver or "folic acid" concentrate and biotin to afflicted animals resulted in the repair of necrotic foci and in the return of degenerated hepatic tissue to normal in a considerable proportion of the animals. This is indicated not only by the difference in incidence of liver lesion in the untreated (A), as compared with the treated (B) group, but also by the fact that 5 rats which showed degenerative lesions at laparotomy, exhibited normal livers following treatment with "folic acid" concentrate plus biotin. Such reparative processes may occur spontaneously, but in a much smaller number of animals, provided that thrombotic vascular occlusions have not resulted in irreparable damage inconsistent with life. It is worthy of emphasis that none of the 5 animals which received liver therapy from the beginning of sulfaguanidine administration showed liver lesion.

The similarity of certain aspects of experimental sulfaguanidine-induced hepatic lesions with those encountered clinically with other sulfonamides makes it appear probable that their etiologic background is identical and that such clinically encountered hepatic lesions may be susceptible to liver or "folic acid" concentrate and biotin therapy. Since liver therapy is already being employed to combat leukopenia incident to sulfonamide administration, the above findings may furnish another reasonable basis for employing this corrective therapy. The questions of whether or not the prophylactic administration of liver or of "folic acid" concentrate and biotin will lessen the incidence of other side effects as well, and whether or not such prophylaxis will interfere with the effectiveness of the sulfonamides, await future clinical investigations.

The basic cause of focal necrosis of the liver which occurs in typhoid fever and occasionally also in other severe infections is not known. It is highly probable that there is severe depletion of the tissue vitamins in these conditions. It is possible that the focal necrosis of the liver in typhoid fever may be caused by infection-induced vitamin depletion and that it may be related to that produced experimentally by drug-induced vitamin depletion. If this be correct, then the focal hepatic necroses secondary to infections may also be susceptible to amelioration by the administration of liver or "folic acid" concentrate and biotin.

The bacterial invasion must be considered an agonal or postmortem phenomenon. The absence of tissue reaction to the presence of the bacteria and the absence of bacteria in any of the animals which did not die spontaneously, support this belief.

There are numerous references in the literature demonstrating the protective effects of various dietary constituents upon the toxic manifestations of certain drugs. The present study emphasizes again the need for careful standardization of the diet in drug toxicity studies. It is evident that the relative amounts of various dietary factors may influence strongly the apparent toxicity of a drug.

The close parallelism between the pathologic alterations of the liver and disturbance in bone marrow functions admits of several explanations. It is possible that the liver produces a factor necessary for leukopoiesis. Disturbance in function of the liver cells, which pre-

cedes or accompanies morphologic alterations of the liver, may depress or inhibit the formation of the leukopoietic hepatic factor(s). Another possibility, which is perhaps more likely, is that chronic sulfaguanidine poisoning produces disturbances in cellular metabolism which are manifested both in the liver and in the bone marrow.

Whatever the explanation, the administration of liver or "folic acid" concentrate and biotin largely corrects the disturbances of cellular metabolism in both the liver and bone marrow as is indicated by the high incidence of normal livers and associated hyperplastic bone marrow in animals so treated.

There is at least one type of cellular metabolic disturbance caused by the sulfonamides which does not appear to be mediated through a vitamin deficiency, and this is hyperplasia of the thyroid gland. Hyperplasia of the thyroid, observed in the present experiment and previously reported by others,^{3,22,23} is prevented or cured by the administration of thyroid powder or thyroxin.^{3,22} This is also indicated by the present results. Apparently the sulfonamides interfere with the production of thyroxin because these animals have a basal metabolic rate below normal in spite of the hyperplastic state of the epithelium.^{3,22}

The collections of large monocytic cells in the lungs may be regarded as an expression of a generalized hyperplasia and mobilization of endothelial cells which reaches its highest development in the liver and spleen. It is true that subpleural foci of endothelial-like cells similar to those found in experimental rats were seen in a number of the control animals. However, the incidence and severity of the lesions were much greater in the animals which received sulfaguanidine than in the controls. The necrotic foci described in human lungs²⁷ secondary to sulfonamide therapy were not observed in the experiments here reported.

Minute focal myocardial necrosis and focal myocardial cellular infiltration incident to sulfonamide administration have been reported in man and animals.^{14,32} In man the cellular myocardial infiltration has been largely eosinophilic.¹⁴ In the present experiments myocardial involvement was minimal and no eosinophils were noted.

With the exception of the basophilic deposits suggestive of calcium salts, the changes in the kidneys are identical to those previously observed with this and other sulfonamides.^{1,16} The interstitial position of this material, usually in what appears to be a lymphatic space, is puzzling and requires further investigation. Randall's theory³⁰ of the genesis of renal calculi receives beautiful experimental confirmation in the presence of masses of the basophilic material beneath the surface epithelium of the renal papilla. Even more striking and confirmatory of this theory are papillary masses of this material covered by epithelium. Some of these papillae are still attached by a narrow pedicle to the renal papilla, while others lie detached as foreign bodies within the renal pelvis.

Conclusions. 1. Rats maintained on a purified basal diet to which has been added 0.5% or 1% sulfaguanidine show severe symptoms and

pathologic changes which become maximal after 2 months of drug ingestion and terminate fatally in about 90% of the animals.

2. The drugged animals show deceleration and cessation of growth and a debilitated general condition. Terminally shock becomes manifest. The signs of this condition are apathy, diminution in body temperature, flaccidity of skin and muscles, failure of cut veins to bleed, and increased viscosity of the blood with increased tendency to clot.

3. The pathologic changes include progressive hypoplasia of the bone marrow which may attain the state of aplasia; degenerative and necrotizing hepatic lesions; focal necrosis and lymphoid exhaustion of the spleen; hyperplasia and mobilization of endothelial cells in the liver, spleen and lungs; hyperplasia of the thyroid gland; occasional minute foci of myocardial degeneration and necrosis with cellular infiltration; urolithiasis with the complications secondary to urinary obstruction; and nephrosis.

4. The administration of liver or "folic acid" concentrate plus biotin to animals suffering from the sulfaguanidine effects reduced the mortality rate from 90 to 14%. Under the influence of this therapy the liver and splenic lesions tended to disappear or to heal and the bone marrow became hyperplastic. The hyperplastic state of the thyroid remained unaffected except by the administration of thyroxin.

5. The experimentally demonstrated curative action of liver and "folic acid" concentrate plus biotin on the toxic sulfaguanidine effects suggests the clinical trial of these preparations as prophylaxis against certain of the toxic effects of sulfonamides. Widespread clinical use of liver or "folic acid" concentrate in sulfonamide therapy must await clinical investigation of the question whether these substances interfere with the effectiveness of the sulfonamides.

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DRUGS USED IN CLINICAL DIAGNOSIS*

REVIEW OF RECENT LITERATURE

THE application of drugs in diagnosis constitutes a chapter of conspicuous importance in the evaluation of disease. Although isolated instances are encountered earlier, it is for the most part a development of the past 25 years. Drugs are used for securing information concerning the structure and function of organs and systems. They have been employed in the study of disorders of the liver, kidney, heart, circulation, central, peripheral and autonomic nervous systems; gastro-intestinal tract, blood, endocrine systems and nutrition. They provide means of ascertaining the powers of absorption, fixation, secretion, excretion and the metabolic state of tissues and organs. The object of the present paper is to review some of the enterprise in this field, more especially those phases which have received particular attention in the past few years.

Bromsulphalein. The dye, phenoltetrabromphthalein sodium sulphonate, was introduced as a test of liver function in 1925 (Rosenthal and White¹⁰²). The test depends on the fact that the compound is almost entirely excreted by the liver into the bile in normal individuals and that in liver dysfunction there is delay in its removal. The principle of the technique involves determining the amount present in the blood at intervals following its intravenous injection. The technique appears to test the capacity of the reticulo-endothelial system (chiefly the Kupffer cells) to remove this foreign substance from the blood stream rather than the capacity of the liver cells to excrete it in the bile. The two functions can be readily separated in the dog (Mills and Dragstedt⁷⁵), and in man (Cantarow and Wirts;¹⁸ Wirts and Cantarow¹³¹). The removal from the blood stream takes place rapidly, 85 to 95 % in 5 minutes, while the excretion in the bile is a matter of several hours. Furthermore, in early bile stasis due to obstruction of the common duct, the excretion of the dye

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into the bile may be delayed while the other function, namely, its removal from the blood stream, may still proceed at the normal speed.¹³¹

There seems to be some doubt concerning the relationship between the blood retention of the dye and the histologic changes in the liver. There is one report which states that abnormal retention is always associated with structural change in the liver as shown by sections of the human liver, although normal retention does not exclude such changes (Bauman and Orr¹³). There is another, however, which states that histologic changes in the liver are not always found to account for the abnormal dye retention (Kruger and Gerber⁵⁰).

In the original test, a dose of 2 mg. per Kg. was injected intravenously and a sample of blood was taken in 30 minutes. The normal standard was complete clearance at this time,¹⁰² the presence of more than traces of the dye in the blood being taken as abnormal. Various modifications have been explored with the view of increasing the sensitiveness of the method. The dose of the drug has been increased, and various plans for testing the blood have been suggested involving one or more samples at intervals varying from 5 to 60 minutes. There remains a great deal of uncertainty in the results of these studies especially because in the case of every modification there is need to revise the standard normal values which are often allowed to rest on an insufficient number of cases. There is the suggestion of increasing the dose to 5 mg. and determining the curve of dye concentration by blood samples taken at intervals of 5 minutes (MacDonald⁶³). The value of this type of curve is in need of further study. The test appears to be more sensitive than the original when made with two blood samples, one at 5 and the other at 15 minutes, the first never showing more than 60% and the second rarely more than 5% retention in normal people (Deutsch²²). There is the indication from comparisons in the same patients that the 5 mg. dose is more apt to detect abnormal liver function than the 2 mg. dose. The larger dose was used with a single specimen of blood tested at 30 minutes (Helm and Machella³⁶), and the assumption was made that the 5 mg. dose of dye disappears from the blood completely in 30 minutes. It was subsequently shown, however, that with this dose about one-fourth of young normal controls retain some dye after 30 minutes, although all show complete disappearance in 45 minutes (Mateer *et al.*⁶⁹).

There is a fairly large literature on the application of bromsulphalein as a test of liver function in various diseases. It has been extended in the past few years. In the test using 5 mg. and 5, 15 and 30 minute blood samples, liver function has been found abnormal in heart failure (Bernstein *et al.*¹⁵) although it is to be noted that the test may prove misleading in heart failure because of incomplete mixing of the dye in 15 minutes.²³ Patients with chronic pulmonary tuberculosis frequently show abnormal dye clearance (5 mg. dose, 15 and 30 minute intervals) and the incidence rises abruptly in those with amyloid disease.⁵⁰ A high incidence of abnormal liver function has been found in a wide variety of cases of low-grade chronic illness (Stiles *et al.*¹¹⁶). These matters are in need of further study because the method used assumed complete clearance of the 5 mg. dose in 25 minutes and others have shown that many normals take longer to clear this dose completely.

Benzoic Acid. The use of sodium benzoate as a means of testing liver function was introduced in 1933 by Quick. It is based on the fact that in man the liver combines glycine with benzoic acid to form hippuric acid which is then excreted in the urine (Quick^{90,91}). Various factors involved

in the interpretation of the test have been studied in recent years. In the way in which the test is applied, one determines the amount of hippuric acid recovered in the urine after a dose of benzoic acid. Since the body does not store glycine (Quick⁸⁹), the amount of hippuric acid recovered tests not only the capacity to conjugate benzoic acid with glycine, but the power of glycine synthesis.⁸⁹ The capacity to synthesize hippuric acid from benzoic acid is limited by the available glycine.⁹⁰ In healthy individuals about 1.5 gm. is the maximum amount of sodium benzoate which the liver can convert into hippuric acid per hour. This peak production is obtained by a dose of 4 gm. of sodium benzoate and cannot be raised by increasing this dose (Probstein and Londe⁸⁶). The simultaneous administration of glycine may greatly increase the hippuric acid excretion (Probstein and Londe;⁸⁶ Quick, Ottenstein and Weltchek⁸³). In view of these facts reduced excretion of hippuric acid after giving benzoic acid may represent either reduced synthesis of glycine or reduced conjugation of hippuric acid. The two functions may be distinguished (Probstein and Londe;⁸⁷ Graña and Vizca²⁹). In one study⁹³ there were 30 patients in whom, after a dose of sodium benzoate, the hippuric acid excretion was less than normal. In most of these the chief difficulty seemed to lie in diminished power to synthesize glycine because the simultaneous administration of glycine raised the hippuric acid recovery. In a smaller number the chief difficulty lay in impaired power to combine glycine with benzoic acid since the simultaneous administration of glycine and benzoic acid did not enhance the recovery of hippuric acid. The use of the hippuric acid test for liver function would be invalid if renal excretion of hippuric acid were slower than the rate of its production. It has been found, however, that the renal excretion of hippuric acid proceeds at a rate about 2.5 times that of its synthesis (Schwei and Quick¹⁰⁶). Since excretion may be diminished in renal disease, the value of the test for liver function may be enhanced by a determination of the rate of excretion of injected hippuric acid (normals, about 3.5 gm. per hour). There are conflicting opinions concerning the question whether the volume of urine affects the excretion of hippuric acid, one study failing to find any relation,⁸⁶ while in another the results indicate a direct relationship (Machella, Helm and Chornock⁶⁷). The rôle of body weight among adults is also undecided, a correlation having been found by one group (Hepler and Gurley³⁸) and denied by another.⁶⁷ A more recent study of the intravenous test has again affirmed a decided influence of the body size on the amount of hippuric acid recovered after the standard dose in subjects without liver disease (Scurry and Field¹⁰⁷).

The original hippuric acid test involved the administration of 6 gm. of sodium benzoate orally and the recovery of the hippuric acid excreted in the ensuing 4 hours in the urine by precipitating and weighing the crystals.⁹⁰ Analytical modifications have been introduced. The solubility of hippuric acid in urine is reduced to one-fifth when the urine is saturated with sodium chloride (Weichselbaum and Probstein¹²⁴). The addition of ammonium sulfate for that purpose seems to be more satisfactory, the loss from dissolved hippuric acid being fairly constant at about 0.1 gm. per 100 cc. of urine (Marron⁶⁸).

It has been suggested that an oral dose of 4 gm. is more satisfactory because it suffices to tax the capacity of the liver fully and has a lesser tendency to cause vomiting than the 6 gm. dose.⁸⁶ A dose of 3 gm. is sufficient for children weighing under 40 kg. (Londe and Probstein⁵⁷). The standard result for normal individuals is the recovery of 3 to 3.5 gm. of benzoic acid as hippuric acid in the urine in 4 hours after an oral dose of

4 or 6 gm. of benzoic acid,^{86,89} or the recovery of 2 gm. or more in 2 hours after the 4 gm. dose.⁸⁶

An intravenous test has also been devised⁹³ (Lipschutz⁸⁶). In the one most commonly used,⁹³ 1.77 gm. of sodium benzoate (1.5 gm. benzoic acid) are injected intravenously in 20 cc. of water. In normal individuals about 50% (0.7 to 0.95 gm.) is recovered in the urine in the form of hippuric acid in 1 hour by the precipitation method. It has been suggested that an ether extract and formol titration method is less likely to yield falsely high values (Moser, Rosenak and Hasterlik⁷⁶). An intravenous method avoids disturbance of digestion and takes less time to complete.

The intravenous hippuric acid test is abnormal in many diseases (Bartels¹⁰): hyperthyroidism, primary liver disease and chronic infectious arthritis. The fact that it is normal in severe muscular dystrophy suggests that muscle plays little or no part in the conjugation of glycine with benzoic acid. The oral test shows the liver function impaired in abdominal operations and after ethylene, ether and spinal anesthetics (Boyce¹⁶). There is impaired liver function not only in primary hepatic disease but in mechanical jaundice and cardiac failure (Lindboom⁶⁵). Psychoses are frequently associated with impaired synthesis of hippuric acid, especially marked in catatonia, these cases showing a rise of synthesis after improvement by treatment (Quastel and Wales⁸⁸). There is some indication that the capacity of the liver to conjugate hippuric acid is related to the severity of hyperthyroidism although the test is not of much value in the management of the disease (Haines, Magath and Power³³). While there may be some correlation between plasma prothrombin and the hippuric acid excretion, the relationship disappears after treatment with vitamin K, indicating that the two functions are independent (Kark *et al.*⁴²). The low hippuric acid values in the test after operation may be due to the diminution in the available carbohydrate (Campbell¹⁷) since glucose administration tends to restore them to normal. In menstruation there is impaired liver function which may be related to the disturbed water balance during this period (Heilig and Kantiengar³⁵). The test also gives low values during pregnancy, especially low in toxemia (Neuweiler,^{77,78} Hirsheimer,³⁹ Palmer⁸⁴).

Patients with 50% reduction in the hippuric acid excretion by this test are poor surgical risks.⁸⁹ While there is some difference of opinion concerning the value of the test in differential diagnosis of hepatic disease and jaundice (Rennie⁹⁵), a normal hippuric acid recovery in the presence of jaundice suggests biliary obstruction and a low recovery points to toxic hepatitis.⁸⁹ This test is more sensitive than bromsulphalein. It has been suggested that it may be too sensitive for practical purposes and that the normal values for the middle and later decades should be lowered (Paulson and Wyler⁸⁵).

Galactose. The use of galactose for the testing of liver function was introduced in 1906 (Bauer¹²). It is based on the fact that this sugar is metabolized exclusively by the liver and independently of insulin (Shay, Schloss and Bell¹⁰⁸). It is converted into glycogen with greater difficulty than other sugars (Cori²¹) and hence is better suited as a test of liver function. Animal experiments show that the liver, and not muscle, converts galactose into glycogen (Uexküll¹¹⁹). It is believed to be superior to levulose or glucose tolerance tests for hepatic function, because tissues other than the liver play a large part in the metabolism of the latter two. The test is carried out in various ways, embodying the administration of the galactose orally or intravenously, and testing either the blood or the

urine after an interval for its content of galactose. In the method of oral administration and urine testing the subject with an empty stomach may receive 40 gm. of galactose in a liter of water. The urine may be collected at intervals of 30 minutes for 4 hours. Two normal values may be obtained under these conditions: less than 3 gm. recovered in the urine and the period for this excretion no longer than 2 hours (Kröncke⁴⁹). The 40 gm. dose is slightly above the maximum which the normal man can metabolize¹² (MacLagan⁶⁴). A maximum strain is therefore put on the liver. A modification in the analytic technique limiting the period of fermentation of the urine to 60 minutes increases the accuracy of the galactose recoveries (Lichtman⁵⁴). Others give 40 gm. orally in as little as 250 cc. of water and test the blood for galactose at intervals of 30 minutes for 2 hours⁶⁴ or the same dose in 400 cc. and test the blood after intervals of 30 and 60 minutes (Althausen, Lockhart and Soley⁴). In normal individuals, after an oral dose of 40 gm., the range of blood concentration is between 10 and 30 mg. per 100 cc., values above 40 and below 10 being considered abnormal⁴ (Meranze, Likoff and Schneeberg⁷²). In one study the normal peak values were found to be higher, between 63 and 81 mg. per 100 cc.,⁶⁴ the blood samples having been taken at 30 minute intervals for 2 hours.

Because of variable absorption there is some question of the reliability of the oral test and intravenous galactose tests have been devised. In one method (Bassett, Althausen and Coltrin¹¹), 1 cc. of 50 % galactose solution per kg. is injected intravenously in 5 minutes and the blood is tested 75 minutes later. In this period normal persons clear the blood completely, while patients with hepatitis retain an average of 45 mg. per 100 cc. and those with obstruction 14 mg. per 100 cc.

The galactose tolerance test is used as a means of revealing hepatic dysfunction in various conditions: cirrhosis of the liver, rheumatoid arthritis, surgical operations and pneumonia, and it serves in the differential diagnosis of toxic from obstructive jaundice.⁶⁴ Abnormality by this test does not run parallel with the results from other tests such as the bromsulphalein or oral hippuric acid tests.⁷²

The test has received special attention in hyperthyroidism (MacLagan *et al.*⁶⁵) and it has been considered of comparable reliability with the metabolic rate in thyroid diagnosis.⁴ Impaired liver function may be demonstrated in from 45 to 90 % of all cases of hyperthyroidism by the various liver function tests, but the galactose test seems to be more uniformly correlated with clinical signs of severity, namely, basal metabolic rate, weight loss, and duration of the disease (Lichtman⁵²). Some have failed to observe correlation of the test with basal metabolic rate.⁴ The galactose retention (oral dose and blood testing) has been found abnormally high in 95 % of cases of hyperthyroidism and abnormally low in about 90 % of cases of myxedema.⁴ It is suggested that rapid absorption in hyperthyroidism and slow absorption in myxedema due to altered speed of phosphorylation in the intestinal mucosa may be responsible for the abnormal values,⁴ although others believe that while the test is an important adjunct to the diagnosis of hyperthyroidism and that this disease rarely exists with a normal galactose tolerance, neither impaired liver function nor altered gastro-intestinal absorption are sufficient to explain fully the mechanism of the change in disorders of the thyroid.⁷² The evidence seems to favor increased rate of intestinal absorption rather than liver damage as the cause of the abnormal galactose tolerance in hyperthyroidism, since in these cases the intravenous test may be normal

when the oral test is grossly abnormal (Barnes and King⁹). Galactose tolerance is abnormal in upper respiratory infections, malignant disease, Bright's disease, and in those who have recently received sulfonamide therapy, but the impairment is most marked in thyrotoxicosis (Rosenkrantz, Bruger and Lockhart¹⁰³). Several of the most recent papers again stress the importance of the galactose tolerance test in hyperthyroidism. It may be used as a diagnostic test (Wilson¹³⁰) in masked thyrotoxicosis, in thyrotoxicosis after iodine treatment, and in cases in which the basal metabolic rate cannot be accurately determined. A normal galactose tolerance helps to exclude hyperthyroidism in patients with elevated metabolism due to other causes; it is more reliable when used in this way because impaired tolerance occurs in a wide variety of disorders. An increased galactose retention as a test for hyperthyroidism is unreliable in the presence of complicating conditions such as have already been mentioned as well as in peptic ulcer, hepatic insufficiency and Paget's disease (Schneeberg, Likoff and Meranze¹⁰⁵).

Bilirubin. The injection of bilirubin as a means of testing hepatic function was introduced in 1927 (Von Bergmann;¹²¹ Eilbott²⁵). The test was developed in this country by Harrop and Barron.³⁴ Evidence is fairly strong that the injected bilirubin is not stored but excreted by the liver. Numerous studies have been made which indicate the value of this test as a measure of the excretory function of the liver (Soffer¹¹⁰). In the conventional method, a dose of bilirubin, 1 or 1.5 mg. per kg., is injected intravenously and the amount remaining in the blood in 4 hours is used as an index of liver function. In many normal people the blood is completely cleared in 4 hours. Some consider excretion impaired if the retention exceeds 5% (Soffer and Paulson¹¹¹), while others accept a retention of 15% or less as normal (Kornberg⁴⁸). A formula has been suggested for calculation which takes into account the fact that the speed of clearance varies with the concentration of bilirubin in the blood, and expresses the result as a "velocity constant of excretion," a method which appears to be especially important for cases with elevated basal concentrations of bilirubin (Weech, Vann and Grillo¹²³). This test of liver function seems to be very sensitive. It was found to be more sensitive than the metabolic tests such as that using galactose or benzoic acid and gave approximately the same number of positive results as the bromsulphalein test in one group of diseases of the liver (White, Deutsch and Maddock¹²⁶). Others have found it even more sensitive, and impaired liver function was found by this test to exist months after recovery from catarrhal jaundice at a time when the bromsulphalein excretion test was normal.⁴³

Tyrosine. The fact long known that there is increased tyrosine in the urine in liver disease (Lichtman⁶³) has been made the basis of a liver function test (Bernhart and Schneider¹⁴). A dose of 4 gm. of tyrosine in a solution of 250 cc. containing 5 gm. of casein is given orally after an overnight fast and samples of blood are tested for tyrosine 1, 2 and 3 hours later. In normal fasting blood the tyrosyl content is equivalent to from 1 to 1.8 mg. of tyrosine per 100 cc. of blood, and rises during the test to 5.4 mg. after 1 hour, falling off in the subsequent 2 hours. In liver disease, it may rise to high levels, 15 mg. in the first hour, and remain high for several hours. The test, in some cases of hepatic cirrhosis, is more sensitive than bromsulphalein and other common liver function tests. Whether the test relates to a metabolic or excretory function of the liver is not yet established.

Amino Acids. In impairment of the liver function in the dog, there is retention of plasma amino acids after the intravenous injection of casein hydrolysate, and this appears to represent a delay in the function of deamination (Goettsch, Lyttle, Grim and Dunbar²⁸). It has also been shown (Lyttle, Goettsch, Greeley, Grim and Dunbar⁶²) that in children with portal cirrhosis similar plasma retention of injected amino acids takes place. Such retention does not occur in nephrosis or in severe kidney disease with impaired renal function. The injected amino acids do not reduce the capacity of the kidney for excretion of the end-products of metabolism of the amino acids, since the urea clearance remains normal; also there is no significant effect on amino acid clearance. In normal children the pre-injection amino acid nitrogen in the plasma ranges from 2.92 to 4.63 mg. per 100 cc., and after an intravenous injection of casein hydrolysate in a dose of 12 mg. of amino acid nitrogen per kg., the normal level is restored in 35 to 95 minutes due to diffusion into the tissues and deamination by the liver. In patients with liver disease there is delay in clearing the plasma of amino acids and there is failure of the normal increase in urinary urea and ammonia excretion following the injection. The injection of amino acids, therefore, seems to provide a method for evaluating the deaminizing capacity of the liver. From a previous study (Stewart and Rourke¹¹³) the conclusion was drawn that in patients with advanced liver disease the non-protein nitrogen level of the plasma returns to the pre-injection value in a manner similar to that of normals after an intravenous injection of a solution of amino acids. These experiments, however, were not so performed as to reveal the delay in the decline of the curve, which appears to be in evidence during the period of the first $1\frac{1}{2}$ hours.

Azorubin-S. This material was first put to use in a test of liver function in 1924 (Tada and Nakashima¹¹⁷). It is a dark red water-soluble dye, which is non-toxic in the necessary doses. It is excreted by the liver to the extent of 95%. A dose of 4 cc. of a 1% solution is injected intravenously, and 5 minutes later 40 cc. of a 25% solution of magnesium sulfate is given through a duodenal tube. Samples of duodenal contents are then collected at 1 to 2 minute intervals. In normals the dye appears in 15 to 30 minutes. Its appearance is delayed in diseases of the liver. The value of this test is confirmed in many studies. It is one of the few dye methods which directly tests the excretory function of the liver, since the method requires its recovery from the duodenum rather than its disappearance from the blood as in the case of bilirubin or bromsulphalein. In a group of cases of cirrhosis of the liver, this test was found as reliable as the bromsulphalein and more often positive than the hippuric acid test, and in early chronic hepatitis it was found more often abnormal than either of the other two (Rosenberg and Soskin¹⁰¹).

Vitamin K. The utilization of vitamin K in the formation of prothrombin is a function of the liver (Andrus, Lord and Moore;⁷ Lord, Andrus and Moore⁵⁸). In the absence of bile in the intestine (biliary obstruction) blood prothrombin falls because of the failure of vitamin K absorption. In hepatic disease blood prothrombin may fall because of diminished capacity of the liver to synthesize prothrombin. In both conditions jaundice may occur. The administration of vitamin K with bile salts causes dramatic improvement in the blood prothrombin in obstructive jaundice (Stewart, Rourke and Allen¹¹⁴). Synthetic vitamin K given intramuscularly is similarly effective (Macfie, Bacharach and Chance⁶⁶). This has been confirmed by many (Scanlon *et al.*,¹⁰⁴ Stewart and Rourke,¹¹⁵

Olson and Menzel⁸⁰). On the other hand, hypoprothrombinemia due to liver disease shows little or no response to vitamin K (Allen and Julian;³ Wilson;¹²⁹ Kark and Souter;⁴³ Smith and Owen;¹⁰⁹ Lucia and Aggeler⁶¹). There is some response to vitamin K if the liver damage is not severe (Rhoads⁹⁷). The response to vitamin K has been suggested as an aid in differentiation of intra- and extrahepatic jaundice (Lord and Andrus⁵⁹). An intramuscular injection of 2 mg. of menadione was found to raise the plasma thrombin 10% or more in 24 hours in patients with extrahepatic jaundice. Several workers have utilized the response to vitamin K as a means of distinguishing surgical jaundice from severe damage of the liver (Olwin;⁸¹ Abbott and Holden;¹ Allen and Julian²). A patient with jaundice who fails to respond to intravenous menadione, 2 mg., repeated in 24 hours, with a considerable increase in the blood prothrombin is not subjected to operation, on the basis that it is in all probability not due to obstruction, but to acute yellow atrophy.⁸¹ The differential response to vitamin K is not absolute and cases of severe jaundice due to parenchymatous liver disease have been encountered which showed good response to vitamin K (White, Deutsch and Maddock¹²⁵). There are many cases of obstructive jaundice in which the extrahepatic disease is complicated by parenchymatous liver disease and in such cases subnormal response to vitamin K occurs (Greene and Bruger³⁰). These factors limit the decisiveness of the test in differential diagnosis of jaundice. Various degrees and types of response to vitamin K have been suggested as means of testing the degree of impairment of liver function (Kark, Souter and Deutsch;⁴⁵ Kark and Souter⁴⁴). Failure to obtain response to vitamin K may be assumed to represent impaired liver function (Owen;⁸² Ziffren, Owen, Warner and Peterson¹³³). Additional information may be secured from the vitamin K response.¹²⁵ The prothrombin may rise rapidly in obstructive jaundice and in healing acute hepatitis, as distinguished from chronic hepatitis; the damage is widespread and irreversible in acute hepatitis if prothrombin continues to fall in the face of an adequate supply of vitamin K.

Multiple Agents in Test of Liver Function. In the past few years numerous studies have been published in which several drug liver function tests were tried in groups of patients with primary liver diseases as well as other conditions in the endeavor to explore their relative sensitiveness and to define better the special uses and applications of the several tests.^{5,6,8,19,22,26,32,37,41,46,47,70,71,73,74,92,94,96,98,100,112,118,120,128} The chief agents represented were benzoic acid, bromsulphalein, galactose, azorubin-S, bilirubin and vitamin K. There have been some comparisons with tests which do not require the administration of an agent such as determination of urinary bilirubin, urinary urobilinogen, cholesterol partition, blood phosphatase, icteric index, Van den Bergh reaction, Hanger's cephalin flocculation test, the Takata-Ara test and others. Opinions which issue from these studies bear on such matters as the effect of age on liver function, the behavior of the liver in various acute and chronic infections, hepatic function in malignant metastasis to the liver, in hyperthyroidism, blood diseases, alcoholism, amyloidosis, heart disease, the use of the tests in preoperative management, as a guide to effectiveness of treatment, and to prognosis, and the differential diagnosis between intra- and extrahepatic jaundice. With respect to many details there is want of agreement arising in part from the differences in technique, limited number of cases in the various groups, and variations in the types of cases studied. Opinions concerning the practical usefulness of liver function tests vary

all the way from those workers who place great reliance on them, to those who find them of little value as a guide either to diagnosis, prognosis or treatment. There is a tendency to ignore the results if they are out of line with the clinical aspects of the case. The sensitiveness of the various tests is ranked differently by different workers. For example, some find the bromsulphalein more sensitive than the hippuric acid test, others find the reverse. Some find the galactose test uniformly successful in differentiating intra- from extrahepatic jaundice; others find it of little value.

It may be well, however, to bring together some of the more important generalizations which seem to be fairly well established by the cumulative experience with these tests in recent years. There seems to be little doubt that with due regard for their limitations, the drug tests for hepatic dysfunction often supply important practical information. The liver has many functions and each of the methods tests a different function. The bromsulphalein test probes the capacity of the reticulo-endothelial system to fix a foreign dye. The bilirubin test probes the capacity of the liver cells to excrete into the bile a normal constituent of the blood; and the azorubin-S test, its capacity to excrete a foreign dye into the bile. The hippuric acid test measures an enzymatic system, the detoxifying power of the liver in the synthesis of glycine and its conjugation with benzoic acid to form hippuric acid. The galactose tolerance tests the glycogenic activity of the liver. Amino acid tests the deaminizing power of the liver. The results of the various tests do not run parallel. In far-advanced liver disease all liver function tests are abnormal, but in lesser degrees of liver damage, impairment is selective and the functional state of the liver is better ascertained from a combination of several liver function tests. Most studies show that in liver disorders impaired glycogenic function as shown by the capacity to metabolize galactose usually comes later than impaired clearance of bromsulphalein, excretion of azorubin-S or bilirubin and synthesis of hippuric acid.

Because these tests are usually designed to throw a maximum load on a liver function, they reveal impaired capacity long before performance has declined sufficiently to produce clinical signs and symptoms. In this way it has become evident that in many diseases, infections and nutritional states, liver function falls off and may play a subtle rôle in the outlook. It has been particularly stressed in Graves' disease and in surgical operations. This is especially significant since it has been found that hepatic function, as revealed clinically and by these tests, may be improved by the administration of glucose and other measures. In general, a normal liver function test is more significant than an abnormal one in a case of suspected liver damage since serious liver damage is not likely to exist in the presence of a normal behavior of these agents in the body. In their application to the differential diagnosis of obstructive and hepatogenous jaundice, the value of the results depends on whether or not the liver is damaged in biliary obstruction. Since the liver is frequently injured in obstructive jaundice, especially when of several weeks duration, the tests are not very helpful except within strict limitations. Under these conditions the finding of normal liver function by these tests is strongly diagnostic of obstructive jaundice. The response of subnormal plasma prothrombin to vitamin K seems to be especially informative in this problem, good response favoring obstruction, poor response hepatitis, and normal response in long-standing biliary jaundice being diagnostic of obstruction. In Graves' disease, although other liver function tests may also be abnormal, the evidence is fairly strong that the galactose tolerance

test is here best adapted to the diagnostic problems, a normal response again being more significant, virtually ruling out hyperthyroidism in a suspected case.

Dextrose. There is an extensive literature on the use of dextrose in diagnostic tests for disorders of carbohydrate metabolism and some on its application to tests of liver function. There have been numerous variations of the techniques for loading the mechanisms concerned with the metabolism of this sugar in the endeavor to simplify the procedure and render the results more informative and reliable. In the past few years studies have been published using the dextrose tolerance test to explore disorders of carbohydrate metabolism in various diseases and some of these will be briefly reviewed.

In a modification of the 2-dose glucose tolerance test of Exton and Rose, it was found that the most important information is to be obtained from the 1-hour blood sample for the diagnosis of diabetes, and from the 2-hour sample for differentiating degrees of severity (Wayburn and Gray¹²²). The 2-dose 1-hour glucose tolerance test often gives results which are in disagreement with the 1-dose method, and the authors in one comparative study conclude that the latter is a more reliable index of diabetes (Langner and Dewees⁵¹). Patients with a diagnosis of non-diabetic glycosuria, based on a single glucose tolerance test, seem to show a higher than expected incidence of diabetes when reexamined several years later, signifying the danger of allowing a final decision to rest on a single glucose tolerance test, especially when the results are borderline (Dewees and Langner²⁴). A new intravenous glucose tolerance test has been developed for distinguishing between benign glycosuria and diabetes mellitus (Lozner, Winkler, Taylor and Peters⁶⁰). After an intravenous injection of 25 gm. of glucose, a blood sugar level which is greater than 120 mg. per 100 cc. after 2 hours indicates diabetes mellitus, while one less than 100 mg. fairly reliably excludes it. An abnormal oral dextrose tolerance test has often been found in patients with mental disorders. In a comparison of the oral with the intravenous glucose tolerance test in patients with manic-depressive psychosis, the results indicate that the abnormal oral test may be a consequence of delayed absorption, since the intravenous test was normal (Gildea, McLean and Man²⁷). The impaired glucose tolerance which is present in patients with pituitary, adrenal, or thyroid disease appears to be related to the fat and carbohydrate content of the diet, and can be altered toward normal by high carbohydrate in the diet. A dextrose tolerance test after a period of high carbohydrate feeding is suggested as particularly important as a means of ascertaining the most favorable period for operation in hyperthyroidism (Greene and Swanson³¹). Marked deviations of the dextrose tolerance tests from the normal are seen in cases of severe burns suggesting, among other things, impaired glycogenic function of the liver (Wolff, Elkinson and Rhoads¹³²). Other liver function tests are also abnormal in severe burns. Marginal malnutrition gives rise to a diabetic-like glucose tolerance test and the diagnosis of diabetes should be deferred in such cases until it is found that the curve fails to return to normal following a period of adequate diet (Robinson, Shelton and Smith⁹⁹). It has been generally taken for granted that the glycosuria and delayed utilization of glucose which occur in obesity represent mild forms of diabetes (John⁴⁰). This has been questioned in a study in which it was found that 77% of adult obese hyperglycemic patients showed a return of the glucose tolerance to normal after adequate reduction of body weight (Newburgh⁷⁹). The sug-

gestion is made that obesity impairs the utilization of glucose in a manner that is independent of any disorder of the insulin mechanism.

The rôle of the liver in carbohydrate metabolism is well known and the fact that in severe liver disease there is hypoglycemia is established. While galactose is now usually employed for testing the glycogenic function of the liver, there are many cases of liver disease in which this test has been found normal, but the glucose tolerance test abnormal (Coller and Jackson²⁰). A fairly characteristic curve was found in liver disease: normal or low fasting blood sugar, rise above normal in first and second hours, and fall to hypoglycemic levels during the third, fourth and fifth hour. There is the belief that both hyper- and hypoglycemia may at times have their origin in a disturbed glycogenic function of the liver, and that hypoglycemia is frequently a surgical problem, arising from damage to the liver from cholecystitis or cholelithiasis. This may be recognized by the glucose tolerance curve. Others deny the usefulness of the test. In children with catarrhal jaundice, no correlation was observed between the type of curve and other tests of hepatic dysfunction (Pachman⁸³). The glucose tolerance curve showed alterations in form and height, and time to return to normal level in patients with gross liver disease, but the results were not sufficiently characteristic or uniform to serve as a basis for the recognition of impaired liver function (Wilson¹²⁷).*

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RADIOLOGY

UNDER THE CHARGE OF

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PULMONARY CYSTS

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IN 1687 Bartholinus reported the first recognized case of the disease which has been called "cystic disease of the lung," "cystic degeneration of the lung," or "pulmonary cysts." In 1925 Koontz¹⁰ reviewed the medical literature and found reports of 105 cases of pulmonary cysts. In 1937 Schenck²⁰ was able to find 381 reported cases. The more frequent recognition of this type of lesion at the present time is due to a great extent to the fact that roentgenologic examination of the thorax now is performed more frequently than it was in the past. In cases in which pulmonary symptoms are due to this condition, the diagnosis can be made only by roentgenographic examination or by exploratory operation. In a relatively large number of cases of pulmonary cysts the patients have no symptoms and it is only by routine roentgenographic examination of the thorax that these lesions are found. Thus roentgenologists who can study the gross character, size, shape and distribution of these cysts should be able to contribute much toward a better understanding of this condition. Conversely the findings of the internists, surgeons and pathologists are of great aid in bringing about a better understanding of these cysts by roentgenologists. It is certain that no one should realize more clearly than the roentgenologist the complexity of the problems involved in trying to understand this perplexing condition.

Some writers, especially Peirce and Dirkse,¹⁶ have objected to the term "cyst" to designate this lesion. They claim that cysts are hollow organs, bladders or sacs which contain liquid secretion, parasitic larvæ or morbid

matter. Thus they felt that only those cysts of the lung which are or have been filled with fluid properly should be called "cysts." This is arguable even on etymologic grounds and relatively unimportant. At any rate by common practice the term "eyst" has for many years been applied to certain air-filled cavities in the lungs, and it is neither possible nor desirable to change the terminology in this respect. When the exact nature of the pulmonary eysts is understood, as is the case in some instances, a more specific term may be substituted, but when the pathogenesis is not understood, the general term "cyst" is still preferable. Some authors have used the term "air eyst" to designate eysts that do not contain fluid.

As pulmonary eysts are seen by the roentgenologist first, it would perhaps be best to consider the appearance of these lesions and their distribution as seen in roentgenograms of the thorax. It would be possible in this way to subdivide them according to their size, shape, number and distribution in the lung. Sellors²¹ classification is quite suitable for this purpose:

1. Solitary eysts—almost invariably of large size.

(a) Huge "balloon" or "distention" eysts, which when they occur in infants cause gross pressure signs and often death.

(b) Smaller cysts about the size of an orange. These often remain "silent" unless infected.

2. Multiple cysts of variable size.

(a) Medium sized, in groups of two or three, close to the root of the lung on occasions. They vary in size from that of a cherry to that of a golf ball. They usually do not cause symptoms.

(b) Small eysts the size of a currant or a cherry.

Multiple eysts may also be divided as:

1. Those which follow a set distribution and which usually are lobar in character. These eysts are uniform in size; they resemble saccular bronchiectasis. Some of these have been called "honey-comb" lung.

2. Diffuse or scattered lesions with cysts of inconstant size: (a) localized patchy distribution; (b) confined to one lung only; (c) scattered through both lungs.

There may be objections to this classification but it is the only one found which is based objectively on the morphology and distribution of the cysts. Certainly, one should not attempt to classify these eysts according to their cause until the great variation in the character of the pulmonary cysts is considered. In other words, one should consider etiologic factors that apply to each type of pulmonary eyst rather than discuss pulmonary cysts as though they comprised a homogeneous group. The failure of most investigators to do this makes a discussion of pathogenesis very difficult.

At first it was thought that all pulmonary eysts were congenital. Both Koontz¹⁰ and Schenck²⁰ expressed this opinion. Anspach and Wolman,¹ who studied pulmonary cysts in infants, regarded them as congenital. Sauerbrueh,¹⁹ who studied bronchiectasis in children, found that 80% of these cysts were congenital in origin and did not cause inflammatory changes in the lung. This congenital bronchiectasis he termed as cystic bronchial disease. Sellors mentioned the similarity between multiple congenital cysts and congenital bronchiectasis. Many other authors have supported the congenital origin of pulmonary cysts.

It would not be suitable here to mention all the theories in support of the congenital origin of pulmonary cysts, which have been well reviewed

by Willis and Almeyda,²⁸ Stanford and Nalle,²⁴ and Gruenfeld and Gray;⁷ especially to be recommended is the paper by Sellors. Some of the theories of the congenital origin, however, will be considered briefly. Anspach and Wolman¹ suggested three ways in which congenital cysts may start. A large cyst may be preformed but collapsed at birth; then it may become distended at the first inspiration. Cysts may develop from small congenital bronchiectatic dilatations which enlarge in postnatal life as the result of stenosis of their orifices. A large air cyst may occur primarily as a large sac which is filled with fluid. The fluid is evacuated spontaneously into the bronchus by rupture of the cyst, which then becomes filled with air.

Anspach and Wolman found pulmonary enterogenous cysts in infants, as did Ward and Krahll.²⁶ These enterogenous cysts are, of course, congenital. They are very rare, but must be considered when a cyst which contains fluid and progressively increases in size is found in a newborn infant. In 1 case reported by Ward and Krahll, a spontaneous pneumothorax developed as the result of the rupture of an enterogenous pulmonary cyst.

Müller,¹⁴ in 1928, in a review of the theories of the pathogenesis of pulmonary cysts, was of the opinion that a bronchiolar bud becomes arrested in its growth before attaining the stage of a hollow tube and that, at a subsequent date, the terminal part begins to grow and forms a closed sac into which fluid is secreted by the lining epithelial cells. He quoted Simpkins, Crosswell and King, and Harris in support of his theory.

These concepts of the congenital origin of pulmonary cysts seem to apply best to certain types which have been described by Sellors. It does seem that some of the "balloon" or "distention" cysts found in newborn infants are congenital in origin. The solitary "smaller cysts which are about the size of an orange," as described by Sellors, also often seem to be congenital. These are usually filled with fluid until they rupture into a bronchus. After this, they contain varying amounts of fluid which may be evacuated at intervals. These solitary congenital cysts are originally, at least, lined with ciliated columnar epithelium and there may be regions of squamous metaplasia. The walls of the cysts may contain glands, smooth muscle, elastic tissue, lymph follicles, and cartilage. Infection may destroy the epithelium. These cysts are often traversed by strands of fibrous tissue.

There is considerable evidence to support the idea that many pulmonary cysts should be considered "developmental" rather than "congenital." According to Miller,¹³ the studies of Broman, Willson, Strukow, and Stefko indicate that the permanent pulmonary parenchyma of the adult develops only after birth and that this development requires from 3 to 14 years; the average time required is about 7 years. Miller expressed the opinion that disturbance in the development of the lung produces both congenital bronchiectasis and congenital cystic lung. He said that arrest of development, whether prenatal or postnatal, means the persistence of the primitive infantile type of lung from childhood into adolescence. The bronchi in such a lung do not branch normally; they become stretched and distended, and develop into bronchiectatic or cystic structures, depending on whether they remain patent or become shut off at their proximal end. Of course, this disturbance in development may result from extrinsic causes; in some cases it is undoubtedly due to pulmonary infection early in life. This concept of the pathogenesis of those types of

pulmonary cysts which resemble or are associated with congenital cystic bronchiectasis seems quite logical.

Willis and Almeyda expressed the opinion that the pulmonary cysts may be either congenital or acquired but they preferred the term "developmental" since they believed that there is usually an underlying weakness of the bronchial or alveolar structures. Examples of cystic lung in cases of familial tuberous sclerosis have been reported by Berg and Zachrisson,³ and Berg and Vejens;² and these pulmonary changes seem to be due to some developmental disturbance. Stanford and Nalle reported a case of emphysematous type of cystic lung which appears to be due to a deficiency in the connective tissue stroma. Koontz quoted Humbert as saying that there are some instances in which there is no deformity at birth but in which there is some defect in the structure of the bronchial walls which later results in malformation. Gruenfeld and Gray⁷ describe how they think multiple cysts can result from developmental variation. They also said that the following theories have been advanced to explain the congenital or developmental nature of pulmonary cysts:

1. Primary agenesis of finer ducts and alveoli (Wolman, Huckel, Grauwitz, DeLange). The cysts are passive dilatations of originally normal air ducts.
2. Neoplastic hyperplasia of the bronchial tree, "cystic bronchoadenoma" (Stoerk, Wermbter, Alth).
3. Hydropic dilatation of congenitally malformed lymph spaces (Virchow, Klebs, quoted by DeLange).
4. Congenital deficiency of elastic tissue (von Hauseman, Dey).
5. Secondary dilatation of air containing ducts due to persistence of congenital atelectasis (Hiller, Sauerbrueh).
6. Fetal bronchopneumonia, mostly syphilitic, leading to stasis of bronchi (Balzer) or to arrested alveolar development (Sandoy).
7. Lobular pneumonia or pneumonitis in childhood, disturbing the differentiation of the pulmonary parenchyma (Miller).
8. Uncoordinated excessive growth of the pulmonary stroma, interfering with the proliferation of the parenchyma, a hamartoma in the sense of Albrecht (Kimla).
9. Stenosis of short segments of the air ducts developing in the prenatal or postnatal period (Eloesser).

With reference to the second and sixth theories, it may be pointed out that, according to the consensus of writers, pulmonary cysts are rarely neoplastic or due to congenital syphilis.

Recently, there has been considerable support given to the concept that pulmonary cysts are acquired and not congenital. Peirce¹⁵ and Peirce and Dirkse,¹⁶ who deserve much credit for stimulating thought in this direction, emphasized that pulmonary cysts are frequently the sequelæ of bronchitis and bronchopneumonia. They expressed the opinion that although congenital cysts may occur they are rare, and that in a very large number of cases the cysts are not congenital. They subdivided cystic pulmonary disease as follows:

- I. True congenital pulmonary cyst or cysts.
 - II. (a) Chronic interstitial pneumonitis with emphysema; (b) chronic bullous emphysema.
 - III. Cystic bronchiectasis.
 - IV. Pulmonary pneumatocele (localized alveolar or lobular ectasia).
- Pulmonary pneumatocele starts as an acute lobular emphysema associated with lobular pneumonia or bronchitis. A persistent check-valve

obstructing the lumen of the bronchus is thought to be due either to non-resolution of the initial inflammation of the bronchus or to a subsequent distortion of the dilated air-spaces. This check-valve type of obstruction of the bronchus has been well described by Jackson.⁸ Cheney and Garland⁶ gave support to the theory that pulmonary cysts are acquired by demonstrating that serial roentgenograms of patients recovering from various inflammatory disease of the lungs, especially pneumonia, disclose an astonishing number of bizarre cystlike lesions. Some of the lesions disappear spontaneously but many remain unchanged. Some increase in size and eventually occupy an entire lobe or even a whole lung. These lesions were called "pneumocysts" by Cheney and Garland,⁶ who said that they represent a bullous-emphysema phase of healing. Caffey⁵ found that in infants with pneumonia there developed, at times, lesions which looked like abscesses, tuberculous cavities or congenital cysts of the lung but which were in reality due to a regional obstructive pulmonary emphysema. They were sometimes multiple. So-called balloon cysts were encountered as the result of this type of regional obstructive pulmonary emphysema, which is a term that can be considered synonymous with pneumatocele. They usually disappeared spontaneously. Some of these acquired lesions greatly resembled solitary congenital cysts.

Maier¹¹ thought that many pulmonary cysts are acquired, although he recognized that congenital cysts are not rare. He also emphasized the importance of recognizing pneumatoceles which follow interstitial pneumonitis. These may disappear more quickly in infants and children than in adults. He found that in children pneumatoceles may attain huge size. Some pneumatoceles remained only a few weeks while others persisted and fluctuated in size for months or years without producing symptoms. He emphasized the importance of distinguishing pneumatoceles from emphysematous bullae since a bulla does not disappear but tends to increase in size slowly, whereas a pneumatocele may rapidly increase or diminish in size and not infrequently will disappear completely and spontaneously. However, if an emphysematous bulla has a constant increase in intracavitary pressure he would call it a pneumatocele, even though it occurred in an emphysematous lung.

There may be difficulty in distinguishing pneumatocele from abscess of the lung. According to Maier, either pneumatocele or abscess may become inflated due to a check-valve action in the bronchus. This inflation of an abscess occurs most frequently in children and infants. Maier emphasized that a pulmonary abscess may persist after the infection has subsided. This is usually due to fibrosis of the surrounding lung but may be due to ingrowth of epithelium. Such an abscess might be confused with an infected cyst.

As Maier has emphasized, emphysematous bullae are an advanced form of emphysema and should not be called cysts. Differential diagnosis is not always easy, however. Weaver and von Haam²⁷ have discussed the mechanism of the development of emphysematous regions which resemble cysts. Caffey has noted the similarity between bullous emphysema and annular cysts. Maier said that if an intrapulmonary air cyst is produced chiefly or entirely by disruption of intra-alveolar septa and if there is little or no check-valve, it is not a pneumatocele but a bullae; however, if the size of the cavity is large, owing to hyperinflation of an originally small cavity, it is a pneumatocele. Maier mentioned that bullae may be difficult to distinguish from pneumothorax. Pulmonary blebs are acute and are usually easily distinguished, according to Maier.

Maier objected to the use of the term "pulmonary cyst" without qualifications. He felt that attempts should be made to distinguish the various types if possible. He said that the formation of a cavity in the lung is a developmental abnormality, is due to destruction of pulmonary tissue by an inflammatory process, is the result of hyperinflation of a small defect in the pulmonary parenchyma, or is due to a combination of these processes. The following is Maier's classification of pulmonary cysts:

I. Non-parasitic cysts and cystlike cavities.

1. Congenital pulmonary cavities.
2. Cystic bronchiectasis.
3. Acquired intrapulmonary cavities originally produced by destruction of pulmonary tissue. The cavity may or may not be epithelialized.
4. Pneumatocele: non-epithelialized positive pressure cavities produced by hyperinflation of a defect in the pulmonary parenchyma resulting from pulmonary infection.
5. Emphysematous bullæ: non-epithelialized pulmonary cavities, produced chiefly by disruption of intra-alveolar septa.
6. Pulmonary blebs: localized collections of air within the pulmonary interstitial tissue.

II. Parasitic cysts.

This classification is very satisfactory. The great difficulty is that it frequently is almost impossible to decide definitely by roentgenographic and clinical methods just how a certain cyst should be classified. The reason for this was well expressed by Smith,²³ who said: "One may hazard the opinion that though the majority of cases are due to some embryologic defect, many are acquired as the result of damage to the bronchi and lungs by previous infection, inhalation of foreign material, or trauma. Given a lung with a developmental fault, or with a residuum of injury of acquired factors, add the interplay of the normal forces which have to do with the mechanics of respiration, namely, traction, pressure effects and drainage, and add to these insults from repeated infections, then there is likely to result a varied pathologic picture in which may be found entrapped air, pocketed fluid, fibrotic formations, pneumonitis, distended and deformed bronchi, and perhaps not rarely a complicating pneumothorax."

Anspach and Wolman¹ made an important point when they said: "Once a cyst has formed its behavior is determined largely by mechanical and accidental influences, such as capsular strength, proximity of adjacent air passages, plasticity of surrounding lung tissue, and the presence or absence of complicating respiratory infections, rather than by its embryogenesis or history of its lining." This is well shown when so-called balloon cysts are considered. Many of these cysts that occurred in infants and were described by Anspach and Wolman appeared to be congenital. However, Caffey⁵ found that some balloon cysts in infants apparently were the result of an inflammatory process and he called them "regional obstructive pulmonary emphysema." Maier,¹¹ Kirklin,⁹ Brown and Brock,⁴ and Cheney and Garland⁶ have reported balloon cysts which probably developed in adult life and which may be called "giant pneumatoceles." The important thing is not whether these were congenital or acquired. The only matter of real importance is that these lesions have a check-valve mechanism in the communicating bronchus which causes the cysts to expand progressively and thus may result in death from respiratory embarrassment.

Rigler¹⁷ has briefly summarized very well the ways in which pulmonary cysts may produce symptoms. These are as follows:

1. There may be loss of lung tissue owing to expansion of the cyst, compression of the remaining lung, and displacement of the mediastinum. Diminished vital capacity may embarrass respiration, especially in children but perhaps also in adults.

2. Infected cysts may cause symptoms of pulmonary suppuration.

3. There may be enlargement of the right side of the heart and cardiac failure.

Tyson²⁵ has found that patients who have solitary pulmonary cysts usually seek relief because of infection or alteration of the mechanical air exchange through a connecting bronchus. Rupture may occur in either case. These infected cysts are often confused with abscesses. The complications occurring in his cases were: (1) infection of the cyst without rupture; (2) infection with rupture and formation of a pyopneumothorax; (3) progressive expansion of the cyst after subsidence of infection; (4) rupture without infection but due to ball-valve effect and formation of tension pneumothorax; (5) rupture of the cyst with discharge of sterile fluid into the pleural cavity.

The surgical treatment of these conditions is not within the scope of this paper, but certain aspects of the surgical treatment are very important and should be considered.

Rigler,¹⁸ Maier,¹¹ Maier and Haight,¹² and Tyson²⁵ have shown how an infected cyst may simulate an empyema; this is especially true if the cyst has ruptured into the pleural space. With an infected pulmonary cyst there is not the pleural reaction that one would expect with empyema. The shape of the cyst, if it has not ruptured, may make its distinction from empyema possible by roentgenographic examination.

It is important to distinguish congenital cysts from non-epithelialized intrapulmonary cavities, such as a pneumatocele, since the latter frequently will disappear spontaneously. If empyema results from the rupture of a congenital cyst it is not sufficient merely to drain the empyema cavity since the epithelialized cyst will not collapse and must be removed. This applies also to infected pulmonary cysts which have not ruptured but have nevertheless been confused with empyema. If empyema does not respond to the usual surgical procedures, one should consider the possibility of a congenital pulmonary cyst. Congenital cysts are lined with columnar epithelium in contrast with the alveolar epithelium, squamous metaplasia or inflammatory tissue which lines bronchiectatic cavities or acquired cysts. The strands of tissue traversing a congenital cyst may be visible in the roentgenogram. The distorted elements of the bronchial wall are often found in the walls of a congenital cyst. Thus biopsy in the course of surgical drainage of an empyema cavity often will disclose the nature of the lesion. If it is a congenital cyst its surgical removal will be necessary. Old abscess cavities of the lung may be lined by bronchial epithelium which has grown in from a bronchus. In this case, the lesion would simulate a congenital cyst but this would make little difference since surgical removal of the abscess would be necessary. Lack of anthracotic pigment within the cyst and in the vicinity of the walls of the cyst has been given by Schenck and Koontz as an indication of lack of function of the tissue and of the congenital origin of the cyst. This might at times be an important point, since the epithelial lining of a congenital cyst sometimes is destroyed by infection.

A tension pneumothorax should be distinguished from a giant pneumatocele which virtually fills the entire lung. Around such a large pneumatocele there can usually be seen some compressed pulmonary tissue,

especially in the apex of the lung and in the costophrenic angle. The hilar shadows are not prominent when there is a balloon cyst whereas in a tension pneumothorax the collapsed lung forms a prominence at the hilus.

It is true that at times the bronchial communication of an air containing cyst cannot be found when the specimen is examined. This is especially true of balloon cysts. Consideration of the physiology of the lung makes it evident that there must be such a communication even though this cannot be seen during examination of the specimen. Anspach and Wolman said that, probably, the communicating bronchiole, entering the cavity by an angular tortuous course, is difficult to demonstrate and by its nature may act as a valve and allow the entrance of air but not its exit.

The use of bronchography with iodized oil in cases of cystic lung is not considered to be of much assistance according to most authors. In most cases the cysts fail to become filled with the oil. Singer²² has used iodized oil to distinguish solitary congenital cyst from empyema. He injected the iodized oil directly into the cavity and then made roentgenograms at many angles and even with the patient upside down. Maier thought bronchography might be of some value in distinguishing a cyst from empyema.

Since cystic bronchiectasis and certain types of pulmonary cysts are very difficult to distinguish and since an infected cyst of the lung would probably require surgical treatment similar to that used for relief of bronchiectasis, it seems that in cases of cystic lung bronchography would be indicated to show the extent and character of the lesion. Solitary pulmonary cysts which are infected are often found to be associated with adjacent bronchiectasis; therefore, bronchography would be indicated to determine the extent and site of the bronchiectasis.

Cavernous bronchogenic carcinoma may have an appearance which roentgenographically is identical with that of an infected solitary pulmonary cyst. Bronchoscopic examination and biopsy will often reveal the presence of carcinoma.

Conclusions. 1. In many cases of pulmonary cysts the pathogenesis cannot be definitely determined.

2. Some pulmonary cysts are congenital in origin.

3. Some pulmonary cysts may be best regarded as "developmental" in origin.

4. Some pulmonary cysts are acquired, usually as the result of pulmonary infection.

5. At times, acquired factors probably cause the development of pulmonary cysts by distorting "developmental" processes.

6. Lesions that may not actually be pulmonary cysts may at times be distinguished with difficulty. This applies especially to emphysema and bronchiectasis.

7. The importance of distinguishing empyema from an infected pulmonary cyst must be remembered.

8. Very large balloon cysts must be distinguished from tension pneumothorax.

9. An infected cyst of the lung should be distinguished from pulmonary abscess, tuberculous cavitation and cavernous bronchogenic carcinoma.

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PHYSIOLOGY

THE CLINICAL SIGNIFICANCE OF THE CAROTID AND AORTIC BODIES

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THE recent discovery of the functions of the carotid and aortic bodies constitutes a major advance in physiology. Although certain details remain to be reinvestigated and reevaluated, there is enough general agreement among physiologists on fundamental concepts to warrant an interpretation of the available data for clinicians. This review will emphasize the *clinical* significance of the carotid and aortic bodies and will merely outline the historical development and anatomic characteristics of these cell groups. Those desiring more detailed information are referred to review articles by several of the original investigators in the field.^{6,26,30,50}

Description of the carotid bodies dates back to 1743, but it was not until 1902 that Biedl and Wiesel⁸ reported a structure which we recognize today as the aortic body. For years these tissues were variously regarded as glands of internal secretion, chromaffin bodies, paraganglia, or cavernous vascular structures. In 1928 de Castro²² shrewdly suggested that on the basis of its peculiar histologic appearance the carotid body might represent a special sense organ capable of perceiving changes in the chemical composition of the arterial blood. This was conclusively demonstrated by Heymans in 1930.²⁹ A similar function was attributed to the aortic body by Comroe¹⁶ in 1939.

A. Physiology. To avoid confusion, one important fact must be established at the outset. The sensory receptors of the carotid and aortic bodies are anatomically adjacent to other receptors which have a some-

what similar name, *i. e.*, the receptors of the carotid sinus and aortic arch. It is unfortunate that the identity of these structures is so frequently confused for, despite their proximity, they have quite different functions. The receptors of the carotid and aortic bodies respond to changes in the *chemical constitution* of arterial blood and should be regarded as *chemoreceptors*. The receptors of the carotid sinus and aortic arch respond to alterations in *arterial pressure* and should be referred to as *pressoreceptors*. Although both groups exert important effects upon respiration and circulation, the results of stimulation of each are diametrically opposed.

It is now well established that stimulation of the sensory receptors of the carotid and aortic bodies leads to increased activity of certain portions of the central nervous system. A first concern must therefore be a consideration of what activates the receptors, together with a discussion of the effects of such activation.

The Stimuli. The chemoreceptors are stimulated by certain changes in the composition of arterial blood:

(a) Decrease in arterial oxygen tension. The distinction between oxygen content and oxygen tension (pressure) is often poorly understood. Oxygen content of arterial blood refers to the amount of oxygen in chemical combination with hemoglobin (normally about 19 to 20 cc. per 100 cc. blood) plus the oxygen physically dissolved in the plasma (about 0.2 cc. per 100 cc. blood). Oxygen tension (pressure) of arterial blood refers to the pressure which the physically dissolved oxygen exerts in the plasma.

The response of the chemoreceptors to a lowered oxygen tension is prompt, intense and prolonged, and represents the organism's chief defense mechanism against anoxia. Whatever resistance the intact individual has against anoxia is due to a flow of afferent impulses from these peripheral receptors, and is not due to a stimulant action directly upon the medullary centers as was formerly believed. This reaction to oxygen deficit constitutes the most important physiologic property of the carotid and aortic bodies.

(b) Increase in acidity.

(c) Increase in carbon dioxide tension.

(d) Increase in blood temperature.

(e) Certain drugs: cyanides, sulfides, nicotine, lobeline, papaverine, etc.

The Response. Increased chemoreceptor activity is evidenced particularly by the response of the respiratory and vasomotor centers. Stimulation of the chemoreceptors results in:

(a) Increase in respiratory rate, depth and minute volume.

(b) Increase in sympathetic nervous system activity: increase in pulse rate, arterial blood pressure, vasoconstrictor tone, and liberation of adrenalin.

(c) Increase in cerebral cortical activity. Evidence obtained from dogs indicates that excessive stimulation of the carotid and aortic bodies produces cortical stimulation which may progress to convulsions.^{47,48} It is possible, therefore, that afferent impulses from these end organs may play a rôle in maintaining cortical function in the face of derangements such as narcosis or anoxia (see page 689). The restlessness of anoxia may be due in part to this factor.

The responses noted above can be maintained for relatively long periods of time.¹³ These receptors are evidently rugged structures which can continue to discharge impulses under conditions which produce marked depression of the central nervous system. This has led Schmidt to regard

the carotid and aortic bodies as the "ultimum moriens" of the respiratory system.⁴⁹

The Rôle of the Chemoreceptors in Normal Man. While the chemoreceptors are important to man during such emergencies as anoxia and acidosis, they appear to have no important function that is demonstrable under normal conditions. Extirpation or denervation of the carotid and aortic bodies in dogs produces no lasting change in the rate, depth, or minute volume of respiration, in B.P.,* pulse, arterial oxygen or carbon dioxide tension or pH. While breathing room air, they behave entirely normally.⁵⁹

Surgical removal of the chemoreceptors has not been performed in man, but one can estimate the degree of their activity by a "physiologic denervation." The inhalation of 100% oxygen probably accomplishes such a denervation for the following reason: If the carotid and aortic bodies of a normal man breathing room air were activated by the oxygen tension of 97 mm. Hg existing in arterial blood,²⁰ this should be a factor in the maintenance of normal respiration and circulation. Inhalation of 100% oxygen, by raising arterial oxygen tension to 670 mm. Hg should abolish this chemoreceptor activity. Since the major function of the chemoreceptors is the response to lowered oxygen tension, removal of this component of chemoreceptor activity should depress respiration and circulation.† However, inhalation of 100% O₂ rarely decreases respiration of normal men and usually increases it about 10%.^{56,59}‡ This indicates that there is no demonstrable tonic chemoreceptor activity in normal man.

However, during certain deviations from normality chemoreceptor function is of undoubted importance. The rôle of the carotid and aortic bodies under such conditions forms the basis for this review. Before discussing their clinical significance, however, the derivation and structural characteristics of these end-organs will be sketched briefly.

Embryology. According to Boyd⁹ the embryologic significance of the carotid body is found in its connection with structures of the third branchial arch. Its primordium is mesoderm of this arch, and its earliest connections are with the artery of this arch and the ectoderm of the glossopharyngeal nerve. The aortic body has a similar origin from the fourth branchial arch and the vagus nerve. There is therefore a clearly defined combination of vascular and neural elements from the outset. The fifth branchial arch is represented in the fetus of some animals by a pulmonary body, but this rarely persists in adult life. Other cell groups (such as the abdominal paraganglia and coccygeal bodies) may respond to chemical changes in the arterial blood; Hollinshead's experiments, which attribute a function of this type to the abdominal paraganglia in mice and rats are of interest in this regard and should be repeated.³¹

* Since the nerve fibers from the carotid sinus pressure receptors and from the carotid body chemoreceptors join and enter the glossopharyngeal nerve, any attempt to block, denervate or extirpate the carotid bodies (in dog or in man) will result in loss of function of the carotid sinuses. This should result in "carotid sinus hypertension." However, the aortic arch pressure receptors can assume the function of the carotid sinuses and maintain a normal level of blood pressure. Since it has been found possible to denervate the aortic body in the dog without damage to the aortic pressure receptors,⁵³ these dogs maintained a normal blood pressure.

† Oxygen inhalation, of course, does not remove whatever tonic discharge might result from receptors activated by the normal acidity, carbon dioxide tension, and temperature of arterial blood, but there is little evidence to indicate that such tonic activity is important.

‡ It is interesting to note that a similar "physiologic denervation" in normal, unanesthetized dogs depresses respiration by 10 to 30% for a period of 1 to 3 minutes, indicative of a minor degree of tonic chemoreceptor discharge. This species difference emphasizes the undesirability of transferring the results of animal experimentation to man.

The occurrence of the carotid and aortic bodies in relation to branchial arches assumes more significance as one considers the respiratory mechanisms of fish.³⁶ Fish take up oxygen from water as it flows through the branchial (gill) system. This branchial respiration in aquatic animals is regulated by the tension of oxygen in the water, a decreased oxygen tension tending to stimulate respiration.³⁷ It seems probable, therefore, that the carotid and aortic bodies in higher forms of life represent the survival of structures which control respiration in water-breathing animals.

Gross Anatomy. A carotid body is situated close to the bifurcation of each common carotid artery. In man the carotid body is about 2 to 3 mm. in its longest diameter and can be demonstrated grossly only with difficulty. Its blood supply is derived from the external carotid artery and its ascending pharyngeal and occipital branches. The nerve supply is the carotid branch of the glossopharyngeal or ninth cranial nerve.

The anatomy of the aortic body in man is less clearly understood, although J. D. Boyd⁹ describes two structures which he regards as homologous to carotid bodies. One of these is found near the innominate artery, usually on its lateral aspect; fibers from the right vagus nerve can be traced to it. The other is situated on the anterolateral aspect of the left portion of the aortic arch; this is closely associated with the left vagus nerve. In the dog and cat, the aortic bodies lie between the ascending aorta and the pulmonary artery and receive their blood supply either from the aorta directly or from the coronary arteries. As a rule, their nerve fibers enter the vagi along with the recurrent laryngeal nerve.¹⁵

Histology. The structure of these bodies is unusual in that the afferent arterics open directly into sinusoidal spaces lined only with endothelium. The cells are arranged in the form of thin anastomosing cords or small cell groups separated from each other, so that each cell is in close relation to the blood stream.⁹ There is a rich nerve supply and an intimate relationship between the nerve endings in the cells and the blood stream. This is of the utmost physiologic significance, creating as it does an optimal situation for reaction to changes in the chemical constitution of the blood.

A knowledge of the histologic structure of the carotid body is also of importance clinically, in that it aids in the diagnosis of carotid body tumors. More than 250 tumors of the carotid body have been reported and these have been referred to as endotheliomas, peritheliomas, neuroblastomas, sympathoblastomas, angiomas, fibroangiomas, sympathetic nevi, adenomas, angiosarcomas, perithelial hemangiomas and paragangliomas.²⁷ This confused terminology can undoubtedly be explained on the basis of the threefold nature of the carotid body, composed as it is of vascular, neural and fibrous tissues. Tumors can arise from any or all of these three tissues, the histologic picture being different in each. As far as we are aware, no tumor formation has yet been described in the aortic body though some mediastinal tumors may conceivably arise from this structure.

B. Clinical Importance of the Chemoreceptors. **ANOXIA.** There is no doubt that man may respond in striking fashion to severe anoxia (see page 682). As has been pointed out, most or all of this response originates in chemoreceptor reflexes. The latter has been demonstrated in dogs by (a) removal or denervation of the chemoreceptors during severe anoxia (in which case respiration and circulation are depressed) and (b) production of anoxia in animals previously denervated (in which case the usual prompt stimulation of respiration and circulation is lacking).

This marked response to severe anoxia and the demonstration of the rôle of the chemoreceptors in anoxia has led some physiologists to believe that the chemoreceptors are of utmost importance in all anoxic states. This is certainly not true. The chemoreceptors are very important, sometimes vitally important, in certain anoxic conditions. In others, they are active but are non-essential to the maintenance of circulation and respiration, and in still other anoxic states, they are not involved at all.

In order to clarify this important point, a classification of clinical anoxia will be introduced which differs from that of Barcroft.⁴ We shall divide anoxic states into only two groups: those in which the *arterial oxygen tension* is *normal* and those in which it is *low*. This division is a logical one, since the stimulus activating the chemoreceptors is a decrease in the oxygen tension of the arterial blood rather than a decrease in oxygen content of whole blood.

I. ANOXIC CONDITIONS WITH A *NORMAL* ARTERIAL OXYGEN TENSION.

Clinical conditions fitting this category are: (a) carbon monoxide poisoning, in which anoxia is produced by reason of the greater affinity of hemoglobin for CO than for O₂, though arterial oxygen tension is normal; (b) methemoglobin formation, as in nitrite, sulfanilamide, acetanilid poisoning, or sulfhemoglobin formation in which functioning hemoglobin is reduced though arterial oxygen tension is normal; (c) anemia, in which the quantity of hemoglobin is decreased but plasma O₂ tension is normal; and (d) certain types of peripheral circulatory failure in which tissue cells may be supplied with less blood per unit time though each unit of blood is well oxygenated (*e. g.*, shock).

Carbon monoxide poisoning illustrates certain principles applicable to this whole group. As indicated previously, because of the great affinity of hemoglobin for CO as compared with O₂ (210:1) only 1/210 as much CO as O₂ is needed in inspired air to enable carbon monoxide to compete on even terms with O₂ and so produce 50% HbCO and 50% HbO₂. Thus the addition of only 0.1% CO to inspired air will produce 50% HbCO and serious poisoning though the oxygen in inspired air will be reduced from 20.93% to 20.91% (a reduction of only 0.15 mm. Hg pO₂—from 159 to 158.85 mm. Hg). Since there has been only an infinitesimal reduction in oxygen *tension*, one would expect minimal or no chemoreceptor activity. However, at the same time, there is a marked reduction in arterial O₂ *content* (to 50% HbO₂). If anoxia were capable of stimulating the chemoreceptors or respiratory center by virtue of a reduction of HbO₂, one would expect to see a definite augmentation of circulation and respiration.

This question was put to a direct test by Chiodi *et al.*,¹⁴ who exposed 4 unanesthetized men to prolonged inhalations of 0.15 to 0.35% carbon monoxide in air. In 13 experiments the HbCO produced was between 30 to 40%, in 9 experiments it was between 40 to 50% and in 1 experiment the HbCO attained was 52%. Nevertheless in none of these 23 experiments was there any change in the minute volume of respiration. Therefore it is evident that the chemoreceptors do not respond to a diminution in the % HbO₂ in the arterial blood. Similar results were obtained in dogs by Comroe and Schmidt.¹⁵

In the human experiments there was no circulatory stimulation until the HbCO rose above 30%; then increases in cardiac output (25 to 30%) and in pulse rate occurred. Since simultaneous increases in blood pressure did not occur, the vasomotor center was probably not stimulated by anoxia; more likely the response was secondary to local peripheral vasodilation caused by tissue anoxia.

This work suggests several important clinical implications: (1) The clinician must not expect a patient moderately or severely poisoned with carbon monoxide to be dyspneic or hyperpneic despite the existence of a dangerous degree of tissue anoxia; it is this feature (along with the presence of a cherry red color—*i. e.*, lack of cyanosis) that makes carbon monoxide one of the most insidious of all poisons. Similarly, in moderate

degrees of anemia, methemoglobin formation, and so on, dyspnea will be lacking. (2) Anoxia stimulates respiration and circulation in man only by reflexes arising in the chemoreceptors. If the chemoreceptors are not stimulated (arterial oxygen tension maintained normal), no respiratory stimulation can be expected from anoxia even though the amount of oxygen carried by the hemoglobin has fallen to 48%. Put in other words, anoxia *does not stimulate the respiratory center directly*.^{*} In fact, Chiodi *et al.*¹⁴ obtained some evidence that anoxia may depress the respiratory center by its direct action: in 2 subjects, inhalation of 2 to 5% CO₂ in air produced 11 to 13% more respiratory stimulation in the normal state than during the period of anoxia caused by CO.[†]

II. ANOXIC CONDITIONS WITH A *SUBNORMAL* OXYGEN TENSION. This group, in which arterial oxygen tension and, as a rule, arterial oxygen saturation are both reduced, includes the great majority of clinical types of anoxia: conditions associated with primary depression of respiration (morphine or barbiturate poisoning, anesthesia produced by pentothal, evipal, avertin, morphine, and so on), breathing of gases with a subnormal oxygen tension (as at high altitudes, or in decompression chambers, during nitrous oxide or ethylene anesthesia, or during nitrogen inhalations in the treatment of dementia precox), and conditions associated with inadequate gas exchange in the pulmonary alveoli (such as pneumonia, atelectasis, pneumothorax, hydrothorax, pulmonary edema, cardiac decompensation, emphysema, asthma, and so on).

1. *Anoxia Associated With Primary Depression of the Respiratory Center.* Marshall and Rosenfeld³⁹ have shown that narcotics depress the respiratory center in the medulla as judged by the inability of these cells to respond to CO₂. Since extreme sensitivity to CO₂ is a dominant factor in the control of normal respiration, one might expect that narcosis would be followed by a decreased minute volume of breathing and the development of arterial anoxemia. This sequence of events occurs during narcotic poisoning and during administration of many anesthetics.

(a) *Narcotic Poisoning.* If an individual has received an overdose of an opiate or a barbituric acid derivative, minute volume of breathing is reduced below normal, oxygen tension in the arterial blood falls and the chemoreceptors of the carotid and aortic bodies are activated. As narcosis becomes more profound, reflexes from the chemoreceptors assume greater

* It may be wondered how the same arterial blood is capable of producing cerebral anoxia without producing chemoreceptor anoxia. This may be satisfactorily explained by referring again to the unusual vascularity of the chemoreceptors which provides these bodies with arterial blood far in excess of their metabolic needs so that dissolved plasma O₂ alone is adequate for metabolic needs. In the brain, the blood flow is more closely adjusted to the oxygen needs of the tissue, and consequently a decrease in O₂ content (without a compensatory increase in blood flow) will lead to an oxygen deficiency of this rapidly metabolizing tissue.

† The fact that anoxia is purely depressant to respiration and circulation has been established previously by numerous investigators using anesthetized dogs with denervated chemoreceptors. However, different results have been obtained if the denervated dogs are unanesthetized or very lightly anesthetized. Under such conditions, anoxia produces the expected depression of respiration, but this is followed in 2 to 5 minutes by an increase above normal.⁴⁹ This increased minute volume, however, is accomplished entirely by an increase in rate; depth being normal or decreased. Since the intact animal responds to anoxia chiefly by an increased depth of breathing, the reaction of the denervated dog represents a distinctly abnormal respiratory pattern. This response differs from that of man, and a species difference again appears to be involved. The presence of other as yet unidentified chemoreceptors in the dog (abdominal paraganglia, cecocolic body) must be ruled out before a definite statement can be made that the respiratory center, even in the dog, is capable of being stimulated directly by anoxia.

and greater importance. The chemoreceptors are stimulated more strongly by increasing anoxia at the same time that the respiratory center is being depressed by the narcotic. When a sufficient degree of central depression has been produced, these afferent impulses may be *entirely* responsible for the maintenance of respiration and perhaps circulation. The control of these vital functions has shifted, in other words, from a delicate sensitive central regulation by CO_2 to a more primitive, resistant, peripheral reflex drive by oxygen lack.

To the physician examining such an individual, this state of affairs may not be evident, unless two diagnostic and prognostic tests are made: (1) Inhalation of 5 to 10% CO_2 *in air*. This will indicate the presence of central depression, since the rate and depth of breathing will not increase, and may even diminish because of the narcotic action of excessive CO_2 . (2) Inhalation of 100% *oxygen*. This will indicate the vital rôle of the chemoreceptors, since respiratory activity will be sharply depressed or may cease altogether, and blood pressure will fall.

These two procedures will indicate to the clinician that the respiratory and circulatory status of his patient is precarious and that a marked degree of narcotic depression exists against which the rugged carotid and aortic chemoreceptors are standing alone.

(b) *Clinical Anesthesia*. The same factors are at work in a patient breathing room air and anesthetized with pentothal, evipal, or avertin. Here, too, as anesthesia progresses, there is a shift in the control of respiration and circulation from the medulla to the chemoreceptors.²⁴ If the anesthetist is not aware of this shift, he may note only the fact that breathing and blood pressure are almost normal and may not appreciate the critical central depression. Failing to realize the significance or even the presence of anoxemia, he may be unprepared for cessation of respiration or sharp decline in arterial blood pressure following the addition of subsequent doses of the narcotic agent.^{5,43}

The situation is analogous to that of a patient who has suffered moderate to severe hemorrhage but whose blood pressure remains practically normal as the result of powerful compensatory reflexes. An additional mild to moderate hemorrhage may at this point produce shock, because compensatory factors are already functioning maximally.

Cyclopropane would produce the same results as pentothal if it were administered with air instead of with high percentages of oxygen. Cyclopropane depresses respiration profoundly only when a chemoreceptor reflex drive is prevented by the inhalation of high oxygen concentrations. Likewise, if pentothal, avertin or evipal were accompanied by inhalations of 100% oxygen, the increased tension of oxygen in the arterial blood would prevent chemoreceptor activity from obscuring the true state of central depression. In this way the full narcotic depressant action would be continually evident and unexpected disasters would be diminished. Since (in the experience of certain Army groups) deaths following pentothal sodium intravenously are 6 to 7 times more frequent than those following other anesthetics,¹⁰ it appears that this knowledge is not generally appreciated.

All narcotics, however, do not lead to anoxemia. Following the administration of ethyl ether, vinethene, chloroform and ethyl chloride, the minute volume of breathing may not be depressed or may even be increased. All of these substances depress medullary centers directly but fail to produce depressed breathing and arterial anoxemia because of the presence of a variety of specific stimulant actions. If these agents are

administered together with a high concentration of oxygen, no reflex chemoreceptor drive can be expected. However, these drugs are irritant in varying degrees to the respiratory mucosa, and may set up reflex drives over the vagus nerves.⁵⁴ There is, furthermore, evidence that ether, at least, may initiate afferent impulses in muscles.¹⁹ Finally, Heinbecker²⁸ and Adrian¹ feel that ether may even have some direct stimulant action in the central nervous system. Whatever the ultimate site of such stimulation, the fact remains that anoxemia does not commonly accompany the administration of these anesthetics (unless respiratory obstruction of some nature occurs), and increased chemoreceptor activity is therefore not a factor. *

It is thus apparent that in anesthesia the chemoreceptors may be of the utmost significance or may play no rôle at all. When arterial anoxemia *does* exist together with narcosis, impulses from the carotid and aortic bodies contribute a great deal towards the maintenance of body function, more perhaps than in any other clinical condition.

2. *Anoxia Associated With Inhalation of Gases With a Low Oxygen Tension.* This is exemplified by an individual breathing low oxygen mixtures at sea level, or by an aviator breathing air at high altitudes. The importance of the chemoreceptors increases progressively with the degree of anoxia. Thus, at an oxygen concentration of 18% in the inspired air (corresponding to an altitude of 3900 feet), practically no evidence of carotid or aortic body activity can be adduced. Most individuals show no increase in respiratory minute volume until a concentration of 14 to 16% oxygen is reached (6900 to 11,000 feet). A few subjects do not even respond to inhalation of 10% oxygen (18,000 feet), although at this level most men increase their respiration by 25 to 35%.²⁵ As the severity of the anoxia increases, the respiratory and circulatory responses may become quite marked. Horvath *et al.*³⁴ reported 1 individual whose respiratory minute volume rose to 65 liters during the inhalation of a 4.2% oxygen mixture. (Even at these low oxygen concentrations, widespread individual variation was noted, ranging from 8 to 65 liters per minute).

At least three major factors are concerned in the response to anoxia. Only one of these, the chemoreceptor reflex, is stimulatory to the medullary centers; the other two decrease central reactivity. Of the factors tending to depress the centers, one is a direct action by the anoxia *per se*. The other is an indirect effect of anoxia: When the chemoreceptor response has produced a vigorous hyperpnea, CO₂ is "blown off" and so arterial CO₂ tension is lowered. This leads to decreased function of the medullary centers and so tends to limit the full magnitude of the stimulant phase of anoxia. It also leads to a shifting of respiratory control from the medullary centers to the chemoreceptors, as in narcotic poisoning.

Severe anoxia produces marked stimulant effects (reflexly), but it produces correspondingly great direct central depression and marked decrease in arterial CO₂ tension. It is for this reason that respiratory failure and circulatory collapse may occur when 100% O₂ is inhaled by men who had been breathing very low oxygen mixtures. This response has been termed "oxygen apnea" or "oxygen blackout."^{39,42,55,57} The sudden withdrawal of the stimulant factor (chemoreceptor reflexes) by the abrupt rise in arterial oxygen tension reveals the presence of the other two factors (direct and indirect depression of the medullary centers). Respiratory and circulatory depression continue until the arterial CO₂ tension rises and/or until the central effects of anoxia have been overcome.

Mild anoxia produces only slight stimulant effects (reflexly) and, unless very prolonged, does not produce significant depression (centrally). Consequently, administration of 100% oxygen to individuals only mildly anoxic is rarely followed by any dramatic change. Even subjects breathing 10% oxygen for short periods of time show only temporary depression of breathing when shifted to high oxygen concentrations. Minute volume of respiration does fall below normal but only for 60 to 90 seconds tending to level off promptly at a figure close to normal.²⁵

It should be emphasized that moderate anoxemia of long duration produces a physiologic state that is closely related to that caused by severe anoxia lasting for shorter periods. It has been demonstrated by Barach³ that in patients with chronic anoxia (cardiac decompensation, pulmonary fibrosis, chronic bronchitis) the administration of high oxygen mixtures might be followed by a "state of stupor, with irrationality when aroused, lasting for 1 to 5 days." These patients seem to have made some adaptation to their anoxic states (the nature of which remains obscure, although it may be related to a chemoreceptor drive to the cerebral cortex or to a compensatory cerebral vasodilation). In any event, the use of high oxygen concentrations leads to deterioration of mental function, and treatment should begin with 30 to 40% oxygen. These patients, interestingly enough, do not develop oxygen apnea when given 100% oxygen, probably because of vagal respiratory stimulant reflexes arising in the diseased lungs.

3. *Anoxia Associated With Pathologic Changes in the Lungs.* These states are even more involved than those previously discussed. In addition to carotid and aortic body reflexes aroused by oxygen deficit, and the central depression outlined above, other factors must be mentioned.^{15,40,52} Most important of these are the Hering-Breuer or vagal lung reflexes activated by unusual distention or collapse of the pulmonary alveoli. These reflexes play a large part in the production of various clinical dyspneas, particularly in asthma, emphysema, pulmonary congestion, and edema. They are initiated by local changes in the lungs and tend to stimulate respiration regardless of the presence or absence of anoxia. Other causes for respiratory stimulation may be sought in the presence of fever (see page 691) or acidosis (see page 690), both of which are accompanied by increase in minute volume of breathing. Finally, in certain pulmonary conditions there may be an elevated CO₂ tension, *e. g.*, emphysema.

Of these five or six mechanisms, which together are responsible for the increased breathing associated with pulmonary disease, only one, the chemoreceptor drive initiated by anoxia, will be affected by oxygen therapy. Since this reflex plays a relatively minor rôle in the cause of clinical hyperpnea,^{15,52} removal of this drive may not be followed by any clinically detectable diminution in respiratory effort. The clinician is thus faced with the paradox of an anoxic, hyperpneic patient, in whom the correction of the anoxia leaves the hyperpnea seemingly unchanged.

This may be explained on the following basis: The hyperpnea caused by the degree of anoxia commonly seen clinically is not marked. The inhalation of 10% oxygen causes a 25 to 35% increase in minute volume, and reduces arterial oxygen saturation to 70 to 80%. Since the arterial oxygen saturation of patients with cardiorespiratory disease does not as a rule fall below 70%, it is evident that the degree of anoxia seen in these disorders produces only small increases in respiratory minute volume (rarely sufficient to cause a subjective sensation of dyspnea). Removal

of this anoxic factor leaves other powerful respiratory stimulant actions unaffected, and leads one to conclude that the chemoreceptors are not of prime importance in the production of clinical dyspnea.

Because of the many complicating factors that may and usually do enter into the clinical picture of anoxia, the response of the anoxic patient to oxygen therapy may appear to be unpredictable and capricious. It is hoped that a clear understanding of the mechanisms discussed above will enable the clinician to evaluate the physiologic state of his patient. In this regard, two points deserve special emphasis: (1) The absence of circulatory or respiratory changes following inhalation of oxygen does not mean that oxygen is without value. Oxygen inhalation often abolishes cyanosis without reducing dyspnea. (2) The occurrence of respiratory or circulatory depression following oxygen administration does not call for an abandonment of this type of therapy. However, one must be prepared for such a response and must carry on respiratory gas exchange artificially for a while, if necessary. Anoxemia is a serious threat to central nervous system and myocardial function. The longer oxygen lack exists, the more likelihood there is of permanent cell damage.

INCREASED ACIDITY. It has been thought for many years that the regulation of normal and abnormal respiration is accomplished by the pH of the arterial blood acting centrally or by the pH in the cells of the respiratory center itself. Two things have occurred in the last few years which appear to invalidate this hypothesis: one was the recent demonstration that respiration is not nearly so sensitive to changes in pH* as formerly believed^{17,44} and the other was the discovery that the carotid bodies (and presumably the aortic bodies as well) *do* respond to changes in arterial pH and apparently are capable of producing a response equal to that of the entire organism. It should be pointed out that the evidence on this score is far from satisfactory, for the simple reason that it is a difficult matter to increase blood acidity without producing simultaneously a change in arterial pCO₂ because of the chemical reaction between acid and bicarbonate. For this reason, it is difficult to evaluate those experiments in which either the brain³³ or the carotid bodies⁵³ have been perfused with acidified blood, and it has been found necessary to perfuse the chemoreceptors with saline solutions (without NaHCO₃) in order to determine quantitatively the uncomplicated effects of acidity upon them. Schmidt, Comroe and Dripps⁵³ performed such experiments in 1939, but since saline perfusions of an organ are admittedly abnormal, the results obtained probably do not indicate the true sensitivity of the chemoreceptors. Nevertheless, it was shown that respiration and blood pressure were increased by decrease in pH of as little as 0.1 unit and were augmented markedly (200 to 300%) by a decrease in pH of 0.4 unit.

The degree of sensitivity of the respiratory center or of the chemoreceptors of man to changes in pH is still uncertain, though there is reason to believe that the response is slight with small changes in pH, yet may be marked with definite uncompensated acidosis. Nielsen⁴⁴ found an increase of only 0.7 L. per minute with a pH decrease of 0.08 unit, and Dennig *et al.*²³ observed an increase of 3.1 L. with a drop of 0.2 pH unit in man.

The conditions in which uncompensated acidosis most frequently occurs

* The recent experiments of Banus *et al.*² purporting to show an extreme sensitivity of the respiratory center to pH changes, cannot be accepted because of the fact that not a single control experiment was performed. Since animals anesthetized with barbital tend gradually to come out of anesthesia, increased respiration is to be expected over a period of time.

are diabetic coma, terminal nephritis, dehydration or starvation, ammonium chloride administration and severe muscular exercise; arterial pH may be lowered just perceptibly or may fall as low as pH 6.98.²¹ In view of the great interest of both respiratory physiologists and clinicians in acidosis, it is amazing to see how few simultaneous measurements of arterial pH and respiratory minute volume have been made in patients. The Kussmaul breathing of acidosis has been frequently mentioned but rarely measured. In cases of severe diabetic or nephritic acidosis with definite fall in arterial pH, respiratory minute volumes of 10.6,⁴⁰ 11.4³⁵ or as high as 55 L. per minute⁴¹ have been recorded. It is possible that this response may be attributable wholly or largely to chemoreceptor activity (though occasionally complicating factors such as fever, pneumonia, or even circulatory failure may contribute to the hyperpnea). In this regard a very interesting observation is that of Schecter,⁴⁶ who reported circulatory collapse following intravenous administration of alkali to patients with severe diabetic acidosis. In light of present knowledge, this may be explained by postulating a depressant action of uncompensated acidosis upon the vasomotor centers counteracted only by reflex stimulation due to the action of decreased pH upon the chemoreceptors; when the reflex stimulation is suddenly withdrawn, due to rapid infusion of NaHCO_3 , the depressed centers are unable to function properly and circulatory failure occurs. Viewed in this way, this accident becomes wholly analogous to the "oxygen apnea" produced by oxygen administration in an anoxic individual (see page 688).

Clinically, therefore the possibility exists that the hyperpnea seen in various types of acidosis may be caused by carotid and aortic body reflexes. Further experiments along this line are indicated.

FEVER. It has been demonstrated clearly in dogs by Bernthal and Weeks⁷ and by Schmidt, Comroe and Dripps⁵³ that warming the chemoreceptors 3° to 4° C. above normal body temperature results in a 33 to 70% increase in respiratory minute volume; cooling the carotid bodies depresses respiration and blood pressure. This respiratory stimulation is characterized by an increase in both rate and depth of respiration and hence is not related to the shallow panting respiration commonly seen in dogs in hot weather. Increased body temperature might also increase respiration in other ways: (a) by stimulation of cerebral centers cephalad to the medulla, (b) by increase in metabolism of the medullary respiratory centers, and (c) by decrease in blood pH resulting from the effect of heat upon blood as a physicochemical system.⁵⁸

It is unlikely that the portion of the hyperpnea of fever (acute infections, severe muscular exercise, and so on) contributed by the carotid and aortic bodies will ever be determined in man. It seems possible, however, that as in anoxic states, the rôle of the chemoreceptors in febrile conditions may become more important during narcosis. This is of particular interest to an anesthetist who commonly uses the to-and-fro carbon dioxide absorbing closed system methods for administering inhalation anesthetics. The temperature of the inspired air rises as anesthesia progresses due to conservation of body heat (by the closed system) and to the generation of heat by the chemical reaction of soda lime with CO_2 . Consequently, rise in body temperature may occur in the anesthetized patient and may contribute, by chemoreceptor reflexes, to the respiratory and circulatory stimulation often observed.

INCREASED CARBON DIOXIDE TENSION. It has been well established^{26,53} that an increase in CO_2 tension acting upon the chemoreceptors will re-

flexly increase respiration, pulse rate, blood pressure and vasomotor tone. It is equally well established that this response requires an increase in CO_2 tension far in excess of that required to stimulate the medullary centers. Therefore small to moderate increases in arterial CO_2 tension will stimulate respiration and circulation without the aid of carotid or aortic body activity.

One might assume that the chemoreceptors, being highly resistant structures, would respond to an elevated arterial CO_2 tension (as well as to anoxemia) after the medullary centers had become so depressed by narcosis or anoxia as to be unable to respond to CO_2 . However, the response of the chemoreceptors to increased CO_2 is not only relatively weak, but appears also to be depressed by the same conditions that depress the central CO_2 response. In this respect, the response of the chemoreceptors to increased CO_2 differs from that to anoxia. Consequently high concentrations of CO_2 do not stimulate reflexly in a subject with depressed centers, and may actually further depress these centers through a direct narcotic action.

From the clinical standpoint, it is apparent that the carotid and aortic bodies are relatively unimportant as far as response to CO_2 is concerned. The threshold of the chemoreceptors is too high and, as CO_2 tension increases in the blood, it is a central rather than a peripheral stimulation which is of major concern.

ACTION OF DRUGS. The first indication that chemoreceptor reflexes were concerned in drug actions was the demonstration by Heymans in 1927 that nicotine could stimulate respiration through reflexes arising in the aorta. Since then a number of other drugs have been found to act on both the carotid and aortic bodies.* Cyanides, sulfides, lobeline, potassium salts, a variety of choline derivatives, and Nikethamide can all be shown to stimulate these end-organs. As far as the mechanism of action is concerned, some facts are evident. The action of cyanide and sulfide is essentially the same as anoxia, these drugs producing oxygen lack through paralysis of cellular respiratory enzymes. Potassium apparently is stimulant to all nerve cells and endings in the body, and its effect on chemoreceptors is one manifestation of this property. Nicotine, lobeline and those choline derivatives with a nicotine-like action, stimulate ganglion cells throughout the body and may stimulate similar cells believed to occur in the carotid and aortic bodies, though recent cytologic studies of Hollinshead indicate that these "ganglion cells" are not nerve tissue but specific "sensory cells."³²

Certain of the drugs acting upon the chemoreceptors are important to the clinician:

1. Several of these drugs have been used to test arm-to-carotid circulation time. The characteristic response of the carotid and aortic bodies to the intravascular injection of stimulant drugs is a gasp. This gasp can readily be detected clinically, and forms the basis for an objective test of circulatory velocity.^{11,38} The drugs (cyanide or lobeline) are injected intravenously, and the onset of the respiratory response noted.

* We must stress again the difference between carotid sinus-aortic arch pressure receptors and the carotid and aortic body chemoreceptors. It is extremely unlikely that drugs act on pressure receptors. Their very nature as stretch organs indicates a response to distention rather than to pharmacologic agents. Despite this, two inaccuracies are current in the clinical literature: (1) drug action on the carotid sinus and aortic arch mechanisms are described on the basis of very sketchy evidence, and (2) authors fail to indicate whether a particular drug action discussed is attributable to the chemo- or pressoreceptors.

The time necessary to transport the drugs from the site of administration to the chemoreceptors is a measure of the speed of the circulation. Recent evidence indicates that papaverine, another substance used to measure circulation time, also produces its characteristic respiratory response reflexly through an action on the chemoreceptors.²⁵

2. Lobeline has been used in an effort to stimulate breathing in newborn infants who are slow to assume normal respiratory activity immediately after birth. The action of the drug, as far as respiratory stimulation is concerned, is upon the chemoreceptors. Because of this, whatever stimulation occurs will be brief and is of value only as a sudden "kick" to a sluggish respiratory center. However, its ability to produce a few gasps may aid materially in expanding atelectatic lungs.⁶⁰ Prolonged stimulation from a single dose of lobeline cannot be expected, and repeated doses should not be given because of the danger of producing depression.

3. Cyanide poisoning: Hydrocyanic or prussic acid blocks oxygen uptake in cells through paralysis of intracellular oxidation. The hemoglobin may be saturated with oxygen; oxygen tension may be normal in the arterial blood, yet tissue death occurs from cellular (histotoxic) anoxia. Initial respiratory and circulatory stimulation are clinical characteristics of cyanide toxicity, and this response is due to a cyanide action of the chemoreceptors. It should be pointed out that only very small doses of cyanide are utilized in the circulation test described above, and that only a transient cellular anoxia is produced in the chemoreceptors, or elsewhere, since cyanide is very rapidly detoxified in the body.

4. The statement has been made that Heymans believed atropine to be depressant to the carotid reflexes. This is an error in interpretation, and has resulted in some erroneous clinical beliefs. Actually, Heymans stated that atropine blocked the cardiac vagus and so prevented the cardiac slowing which otherwise followed stimulation of the carotid *sinus*. In 1941, Burstein¹² concluded that atropine and scopolamine depressed chemoreceptor response and that the use of these drugs, so commonly employed in the preoperative period was hazardous. Phelps also regarded atropine as a depressant to the chemoreceptors.⁴⁵ Evidence that atropine has no action on the chemoreceptors was provided by Schmidt and Comroe.¹⁸ Burstein's results are not questioned, but they can be explained on an entirely different basis. Atropine should therefore not be regarded as depressant to the carotid and aortic bodies.

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BOOK REVIEWS AND NOTICES

VIRUS DISEASES IN MAN, ANIMAL AND PLANT. A Survey and Reports Covering the Major Research Work Done During the Last Decade. By GUSTAV SEIFFERT. English translation by MARION LEE TAYLOR, PH.D. Pp. 332; 7 figs.; 7 tables. Published upon recommendation of the National Research Council. New York: Philosophical Library, 1944. Price, \$5.00.

THIS book is a fairly complete review of the more important works in the vast literature on virus research up to about the year 1937. The aim of the author is to present an introduction into the virus field for those who wish to study it quite thoroughly. References are made to reviews or important publications on each virus and virus disease covered in the text.

The text embodies 5 divisions: (1) a general concept of viruses and virus diseases; (2) specific virus diseases (some covered completely, others merely mentioned); (3) virus-like organisms, including the Rickettsia, Bartonella, Pleuropneumonia and others; (4) filterable types of bacteria; and (5) methods of virus investigation. (This is recognized as incomplete by the author.)

The rapid advances in virus research since 1937 seems to call for a more recent review text of this type to supersede or supplement this text, although many of the fundamentals of knowledge on virus diseases were uncovered before this publication. In some parts the text is awkward and not clearly presented, probably because of a too literal translation by someone not too familiar with virus or medical terminology. The references to other publications were not without error. While not complete, however, this review text does give the student of viruses (vira) an insight into the important advances in his field.

F. E.

THE DIET THERAPY OF DISEASE. A Handbook of Practical Nutrition. By LOUIS PELNER, M.D., Assistant Attending Physician, Long Island Hospital, Greenpoint Hospital, and Brooklyn Cancer Institute; Gastroscopist, Beth Moses Hospital; Lecturer, Post-Graduate Course in Gastroenterology, under the charge of Dr. S. A. Seley. Pp. 143. New York: Personal Diet Service 1944. Price, \$3.75.

"THE Diet Therapy of Disease" is, as the author states in his Preface, a somewhat ambitious title for this book. It is rather a compilation of some of the diets that are used by the Personal Diet Service of which the author is editor. The book contains 44 diets for some 25 different conditions, each being preceded by a short résumé of the physiology of the disease. The concise form of the diets and the ease with which they can be understood may be of some value to the busy practitioner, but the preliminary discussions are confused, contradictory, and filled with grammatical errors. Not all of this can be blamed on poor type-setting or careless proofreading; for instance, the author speaks (p. 16) of certain essential fatty acids "such as arachidonic and perhaps linoleic and linoleic acids" when he obviously intends one of them to be linolenic. It seems to the Reviewer that little excuse can be offered for the publication of such a book.

E. B.

THE MICROSCOPE. By R. M. ALLEN. Third printing. Pp. 286; 17 plates; 82 figs. New York: D. Van Nostrand, 1944. Price, \$3.00.

THE medical sciences owe a tremendous debt to the microscope. Many of their advances could not have been made without it. This book has been written in such a way that the theory and manipulation in microscopy might be understood by even those with little technical training. The author has

not intended the text to be an encyclopedia on microscopy and so treats only the essential details on each subject.

There are chapters on the historical background, optical principles, descriptions and analyses of the types of modern instruments, methods of illumination, methods for testing microscope objectives, how to get the most out of a microscope and preparation of material for microscopic examination. One of the most instructive is the chapter on Getting the Most Out of the Microscope. The author presents hints for both the beginner and expert on how to increase the potentialities of his microscope.

Here is a book that would be of great value to everyone who uses a microscope in his work. It could act as a guide in the choice of a new instrument as well as in testing the value of his laboratory equipment. By following the principles suggested by the author, one could easily increase the value of his standard equipment and his ability in its use. A text of this type could have tremendous value in teaching institutions where the fundamentals of microscopy should be implanted correctly. This book should be had in all teaching and research laboratories as a guide in the technique of microscopy. F. E.

PHOTO-MICROGRAPHY. By R. M. ALLEN. Pp. 265; 50 plates; 175 figs. New York: D. Van Nostrand, 1941. Price, \$5.50.

EVERYONE in science who uses a microscope in his work has at one time or other come upon some microorganism, some field in a histologic section, or pathologic lesion, a chemical crystal or other microscopic structure which he would like to include in his permanent records. In answer to his needs the author of "The Microscope" has written an authoritative text which explains all the fundamentals in photography as taken through a microscope. It is not written in complicated terminology but in a way that all scientific workers can understand and apply the methods explained.

There are chapters on fundamentals, modern equipment, homemade equipment, technique of photomicrography, special applications ranging from metallography through to the electron microscope, microphotography (microfilm), photographic processes, materials and equipment, as well as a series of 50 representative photomicrographs showing what can be done in many fields by applying methods as described in the text.

This text should be of great use for all laboratories using photography in their microscopic work. Especially important for most laboratories are the sections on "Homemade Equipment" and "The Technique of Photomicrography." It is not every laboratory that can afford the complete equipment or a full-time photographer trained in such methods. Here is a book giving the methods and techniques that one can use to complete a microphotographic set-up for his own laboratory with the minimum time and effort as well as to train himself to become highly proficient in photomicrography. This book cannot be too highly recommended. F. E.

A BIO-BIBLIOGRAPHY OF ANDREAS VESALIUS. By HARVEY CUSHING, M.D.; Preface by JOHN F. FULTON, M.D. Publication No. 6—Historical Library of Yale Medical Library. Pp. 229; 89 figs. New York: Schuman, 1943. Price, \$15.00.

THE HARVEY CUSHING COLLECTION OF BOOKS AND MANUSCRIPTS. Publication No. 1—Historical Library of Yale Medical Library; Preface by JOHN F. FULTON, M.D. Pp. 207. New York: Schuman, 1943. Price, \$8.50.

LOVERS of beautiful books and devotees of the history of medicine had good reason to mourn when Paul Hoeber passed from the scene. Now, however, they have equally good grounds for hope that a similar rôle may be filled by Schuman's of New York. Certainly these two Cushing books—both publications of the Historical Library of the Yale Medical Library—set a standard of distinction and excellence that leaves little to be desired.

The Bio-bibliography of Andreas Vesalius—the more important of the two—

is the fruition of Dr. Cushing's many years of study of the man and his works. In the Preface, Dr. Fulton dates this interest from 1898 or earlier; incidentally I recall, some years after that, Cushing mentioning that he hoped he might some day produce an English translation of the *Fabrica*. This was not to be, and even the Bio-bibliography, which he hoped to have published for the quadricentennial of the *Fabrica*, was apparently far from finished at his death in 1939. We, and the book itself, owe much therefore, to Drs. Fulton, Francis and Castiglioni, Mrs. Peters and others for completing, revising and editing the text. In spite of these difficult times, they have attained Dr. Cushing's goal of publication in 1943, the Vesalius Anniversary year.

We are given a good background of preliminary pages to prepare us for the Bio-bibliography proper. Following a sensitive and appreciative Preface by Fulton, the author offers a characteristically lively apologia—would that it had been longer! Next come a few pages to "place" Vesalius (but why call them Bio-bibliography?); more on Vesalius and Calcar, and Cardan's Horoscope of Vesalius, and then the main text. This is divided into chapters, one for each of Vesalius' 7 works; one (by Castiglioni) on Fallopius and Vesalius, and one on Vesaliana compiled by Mrs. Peters. Valuable to all who are interested in Vesalius—and what lover of medical history is not?—this book becomes an absolute necessity for students of that great figure.

THE second volume, a short title catalogue of the Harvey Cushing Collection of Books and Manuscripts, now in the Medical History branch of the Yale Library, was made possible by a bequest in Dr. Cushing's will. When the Catalogue is supplemented, as is the intention, by similar catalogues of the Klebs and Fulton collections in the same library, a tool for students of medical history both in and outside of New Haven will have been created that will be equal to or perhaps even surpassing the celebrated *Bibliotheca Osleriana*. The items are divided into 5 classes: Manuscripts, Orientalia, Incunabula, General Works (comprising the great bulk of the contents), and Cushing Memorabilia. The job has been carefully done by trained librarians; unavoidable inconsistencies are recognized and avoidable ones avoided. Frequent citations to this or that reference work are given for those seeking fuller details, in the case of items published before 1800. Thus is one more item added to Yale's beautiful Medical History Library on the road toward fulfilling its destiny as a focus for productive scholarship.

E. K.

FUNDAMENTALS OF PSYCHIATRY. By EDWARD A. STRECKER, M.D., Sc.D., F.A.C.P., Professor of Psychiatry and Chairman of the Department, School of Medicine, Univ. of Penna.; Psychiatrist to the Pennsylvania Hospital; Attending Psychiatrist, Philadelphia General Hospital; Consultant to the Bureau of Medicine and Surgery, U.S.N.; Consultant to the Secretary of War, A.A.F. Second ed. Pp. 219; 15 figs. Philadelphia, London, Montreal: J. B. Lippincott, 1944. Price, \$3.00.

THE 2nd edition of this little book needs no revision. It is a concise and well-written account of the psychosis and psychoneuroses as they occur in peace and war. The chapter on classification should help all those not well versed in the nomenclature of mental illness. A glossary of terms, uniquely printed on the end papers, is most useful. The value of the book is in inverse proportion to its pocket size.

H. S.

THE AMERICAN ILLUSTRATED MEDICAL DICTIONARY. By W. A. NEWMAN DORLAND, A.M., M.D., F.A.C.S., Lieut. Colonel, M.R.C., U.S.A.; Member of the Com. on Nomenclature and Classification of Diseases of the American Medical Association; Editor of "American Pocket Medical Dictionary." With the collaboration of E. C. L. MILLER, M.D., Medical College of Virginia Twentieth ed. Pp. 1668; 885 illus.; 240 portraits. Philadelphia and London: W. B. Saunders, 1944. Price, plain—\$7.00; Thumb-indexed—\$7.50.

PERUSAL of successive editions of our leading medical dictionaries invariably produces in this reader the same two responses: (1) what accurate, up-to-date,

inclusive and conveniently helpful books they are; (2) how difficult it is to make a choice between them. This latest edition of "Dorland" contains hundreds of new words not to be found in any other similar work, but the same could probably be said of "Stedman," if a new edition should happen to come out in the next year or two. It is also noteworthy that the terminology in this edition conforms to that of "The Standard Nomenclature of Diseases and Operations." "Dorland's" specializes on useful lengthy groupings of many items, often eponymic, in such categories as Diets (2 columns), Diseases (13 columns), Methods (14 columns), Syndromes (10 columns), and so on. A list of these and of Tables used occupies a full page just after the Preface. Naturally, many of these words included have never been of any importance and may be quite obsolete, but these may be just the ones that are hardest to trace elsewhere; and it should be remembered that a dictionary exists primarily to inform the seeker and not to educate.

Twenty editions in 45 years go far toward demonstrating not only the need for such books but also the rapid progress of a science that requires such frequent revisions, and the value of such a nest egg for a medical publisher!

E. K.

VASCULAR RESPONSES IN THE EXTREMITIES OF MAN in Health and Disease.

By DAVID I. ABRAMSON, M.D., F.A.C.P. Pp. 412; 59 figs.; 4 tables. Chicago Univ. of Chicago Press, 1944. Price, \$5.00.

THIS is a splendid contribution to a rapidly growing field. The author has used a dynamic approach which permits critical judgment on therapeutic measures from the functional standpoint. Various forms of treatment can now be evaluated on the basis of sound pharmacologic and physiologic grounds rather than on the more empirical and less scientific clinical approach. The book should prove a great stimulus to investigators of normal and abnormal circulation. Experimental methods are outlined critically, and gathered together for the first time.

For the clinician, there is perhaps insufficient detail in the sections designated "clinical application." In many of these, drugs are considered without dosage schedules (*e. g.*, the use of papaverine as a vasodilator) in the case of hypertonic saline solution the amount to be employed is not given, etc. A more complete outline of the various therapeutic measures suggested would be helpful.

R. D.

NEW BOOKS

Malaria: Its Diagnosis, Treatment and Prophylaxis. By WILLIAM N. BISHAM, Colonel, U. S. Army, Retired. Pp. 197. Baltimore: Williams & Wilkins, 1944. Price, \$3.50.

Plaster of Paris Technic. By EDWIN O. GECKELER, M.D., Associate Professor of Orthopaedic Surgery, and Chief of the Fracture Service, Hahnemann Med. Coll. and Hosp., Philadelphia; Fellow of the Am. Coll. of Surgeons, Fellow of the Am. Acad. of Orthopaedic Surgeons, Fellow of the Am. Assn. for the Surgery of Trauma, Diplomate of the Am. Board of Orthopaedic Surgery. Pp. 220; 208 figs. Baltimore: Williams & Wilkins, 1944. Price, \$3.00.

The Urinary Tract. A Handbook of Roentgen Diagnosis. By H. DABNEY KERR, M.D., Professor of Radiology, State Univ. of Iowa Coll. of Med., and CARL L. GILLIES, M.D., Associate Professor of Radiology, State Univ. of Iowa Coll. of Med. Pp. 320; numerous figs. Chicago: Year Book Publishers, 1944. Price, \$5.50.

Poisonous Plants of Hawaii. By HARRY L. ARNOLD, M.D., Honolulu. Pp. 71; 24 plates. Honolulu, Hawaii: Tongg Publishing Co., 1944.

Hipertension Arterial Nefrogena. By EDUARDO BRAUN-MENENDEZ, JUAN CARLOS FASCILOLO, LUIS F. LELOIR, JUAN M. MUNOZ, and ALBERTO C. TAQUINI. Instituto de Fisiologia de la Facultad de Ciencias Medicas de Buenos Aires; Instituto de cardiologia Fundacion V. F. Grego. Pp. 462; 93 figs. Buenos Aires: Liberia y Editorial "El Alteneo," 1943.

Cataract and Anomalies of the Lens. Growth, Structure, Composition, Metabolism, Disorders, and Treatment of the Crystalline Lens. By JOHN G. BELLOWS, M.D., PH.D., Assistant Professor of Ophthalmology, Northwestern Univ. Med. School, Chicago. Pp. 624; 208 figs.; 4 color plates. St. Louis: Mosby, 1944. Price, \$12.00.

Advances in Protein Chemistry. Edited by M. L. ANSON, Continental Foods. Hoboken; JOHN T. EDSALL, Harvard Med. School, Boston; and 9 Contributors. Vol. 1. Pp. 341; numerous figs and tables. New York: Academic Press, 1944. Price, \$5.50.

Vitamins and Hormones. Advances in Research and Applications. Edited by ROBERT S. HARRIS, Associate Professor of Nutritional Biochemistry, Massachusetts Inst. of Technology, Cambridge, Mass.; KENNETH V. THIMANN, Associate Professor of Plant Physiology, Harvard Univ., Cambridge, Mass. Vol. 2. Pp. 514; numerous figs. and tables. New York: Academic Press, 1944. Price, \$6.80.

A Textbook of Pathology. Pathologic Anatomy in Its Relation to the Causes, Pathogenesis, and Clinical Manifestations of Disease. By ROBERT ALLAN MOORE, Edward Mallinckrodt Professor of Pathology, Washington Univ. School of Med., St. Louis. Pp. 1338; 513 figs.; 34 in color. Philadelphia and London, Saunders, 1944. Price, \$10.00.

Our American Babies. The Art of Baby Care. By DOROTHY V. WHIPPLE, M.D. Introduction by C. ANDERSON ALDRICH, M.D., Chief of Staff, The Children's Memorial Hosp., Chicago. Pp. 367; numerous figs. and tables. New York: M. Barrows, 1944. Price, \$2.50.

Women and Men. By AMRAM SCHEINFELD, Author of "You and Heredity." Pp. 453. Illustrations by the Author. New York: Harcourt, Brace, 1944. Price, \$3.50.

An intelligent, and apparently accurate presentation for the laity.

The Medical Clinics of North America. Symposium on Specific Methods of Treatment. The Boston Number. 22 Contributors. Pp. 1292; 96 figs. Philadelphia and London: Saunders, 1944.

Surgery of the Hand. By STERLING BUNNELL, M.D., Honorary Member of Am. Acad. of Orthopedic Surgeons, Member of Am. Assn. of Plastic Surgeons and of Am. Soc. of Plastic and Reconstructive Surgery, Licentiate of Am. Board of General Surgery and Plastic Surgery. Pp. 734; 597 illus. Philadelphia, Lippincott, 1944. Price, \$12.00.

Mitosis. The Movements of Chromosomes in Cell Division. By FRANZ SCHRADER, Professor of Zoölogy, Columbia Univ. Pp. 110; 15 figs. New York: Columbia Univ. Press, 1944. Price, \$2.00.

We are unimpressed.

D. C.

NEW EDITIONS

Diseases of the Digestive System. Edited by SIDNEY A. PORTIS, B.S., M.D., F.A.C.P., Associate Professor of Medicine, Univ. of Illinois Med. School (Rush); Attending Physician, Michael Reese Hosp.; Consulting Physician, Cook County Hosp.; Consultant in Medicine to the Inst. of Psychoanalysis, Chicago. Second Ed. Pp. 932; 182 illus. Philadelphia: Lea & Febiger, 1944. Price, \$11.00.

The Radiology of Bones and Joints. By JAMES F. BRAILSFORD, M.D., PH.D., F.R.C.P., F.I.C.S. Third Ed. Pp. 440; 404 illus. Baltimore: Williams & Wilkins, 1944. Price, \$12.00.

The Diseases of the Endocrine Glands. By HERMANN ZONDEK, M.D. (BERLIN), Director of the Medical Division, Bikur Cholim Hosp., Jerusalem; Late Extraordinary Professor of Medicine in the Univ. of Berlin and Director of the Medical Division of the Krankenhaus Am Urban in Berlin. Translated by CARL PRAUSNITZ GILES, M.D. (BRESLAU), M.R.C.S. (ENG.), L.R.C.P. (LOND.), Late Honorary Research Fellow, Victoria Univ. of Manchester; Late Professor of Hygiene and Bacteriology, Univ. of Breslau. Fourth (second English) Ed. Pp. 496; 178 figs. Baltimore: Williams & Wilkins, 1944. Price, \$11.00.

Recent Advances in Anæsthesia and Analgesia (Including Oxygen Therapy). By C. LANGTON HEWER, M.B., B.S. (LOND.), D.A. (ENG.). Fifth Ed. Pp. 343; 141 figs. Philadelphia: Blakiston, 1944. Price, \$5.50.

Principles of Chemistry. An Introductory Textbook of Inorganic, Organic, and Physiological Chemistry for Nurses and Students of Home Economics and Applied Chemistry. By JOSEPH H. ROE, PH.D., Professor of Biochemistry, School of Med., George Washington Univ.; Formerly Instructor in Chemistry, Central School of Nursing, Washington, D. C. Sixth Ed. Pp. 403; 47 figs.; 4 color plates; 15 tables. St. Louis: Mosby, 1944. Price, \$2.75.

A Laboratory Guide in Chemistry. By JOSEPH H. ROE, PH.D., Professor of Biochemistry, The School of Med., George Washington Univ., Washington, D. C.: Pp. 191; numerous illus.; 2 color plates. St. Louis: Mosby, 1944. Price, \$1.00.

A Textbook of Histology. Functional Significance of Cells and Intercellular Substances. By E. V. COWDRY, Professor of Anatomy, The School of Med., Washington Univ., and Director of Research, The Barnard Free Skin and Cancer Hospital, St. Louis, Mo. Third Ed., thoroughly revised. Pp. 426; 317 figs.; 13 in color. Philadelphia: Lea & Febiger, 1944. Price, \$7.00.

Child Care and Training. By MARION L. FAEGRE, Assistant Professor of Parent Education, and JOHN E. ANDERSON, Director, Institute of Child Welfare, Univ. of Minnesota. Sixth Ed., revised. Pp. 314; numerous illus. Minneapolis: Univ. of Minnesota Press, 1943. Price, \$2.50.

Atlas of Dental and Oral Pathology. Prepared at the Army Institute of Pathology of the Army Medical Museum Office of the Surgeon-General, Washington, D. C. From Material in the Registry of Dental and Oral Pathology by JAMES B. MANN, Col., Dental Corps, U.S.A., Former Pathologist to the Registry; J. E. ASH, Col., M.C., U.S.A., Curator; JOSEPH L. BERNIER, Major, Dental Corps, U.S.A., Former Pathologist to the Registry. Third Ed. Revised by HENRY M. GOLDMAN, Lt., Dental Corps, Pathologist to the Registry. Pp. 310. Washington: American Registry of Pathology, 1944.

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ORIGINAL ARTICLES

MYASTHENIA GRAVIS TREATED WITH LARGE DOSES OF NEO- STIGMINE METHYLSULFATE, INTRAMUSCULARLY AND INTRAVENOUSLY, AND WITH NEOSTIGMINE BROMIDE ORALLY*

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SINCE the discovery by Walker^{11,12} of the efficiency of neostigmine (prostigmine) in the treatment of myasthenia gravis, the drug has been used extensively, both orally in the form of neostigmine bromide and parenterally as neostigmine methylsulfate. Most patients are maintained on oral medication, as first reported by Everts² and subsequently by Laurent and Walker,⁵ Viets, Mitchell and Schwab,¹⁰ and many others. Recently Viets⁹ has emphasized the need in some cases for large oral doses up to 25 tablets in 24 hours (375 mg.), and reported upon one patient who had been maintained on this intake daily for more than 2 years without untoward effects. The use of neostigmine bromide in such large amounts greatly exceeded the dose of 45 mg.,^{6,7} usually recommended, but Viets⁹ found the average amount used by 45 patients in his clinic to be 163.5 mg. in 24 hours. No ill effects from taking these amounts over periods of years had been noted. The patients did not become tolerant to the drug, and, when spontaneous remissions in their symptoms of myasthenia gravis appeared, the patients were quickly able to reduce their maintenance intake, or, in some favorable cases, to omit the drug entirely for varying periods of time. That neostigmine is relatively less toxic than originally considered, especially by Goodman and Bruckner,³ is now fully realized.

The amount of neostigmine methylsulfate, given parenterally, has also greatly exceeded the dose ordinarily used, although no reports have appeared in the medical literature on this aspect of the treatment of patients with myasthenia gravis. Such a case has recently been observed. The drug was used both intramuscularly and intravenously in large amounts.

Case Report. History. A. J. T., a married man of 68, American, was admitted to this hospital on May 21, 1943, because of progressive general

* The neostigmine was furnished by Hoffmann-La Roche, Inc.

weakness, diplopia, dysphagia and dysarthria of 8 months' duration. His first symptom, in September, 1942, was diplopia; ptosis followed in January, 1943. By February he had difficulty in moving his shoulders, lifting his head off the bed and holding up his jaw. Swallowing weakness and nasal speech developed shortly. When attempting to swallow liquids, the fluid escaped through his nose. A test,⁸ with the diagnostic ampule of neostigmine methylsulfate, was positive for myasthenia gravis, all symptoms of muscle weakness disappearing promptly. On oral medication of 6 to 10 tablets of neostigmine bromide, 15 mg. each, spaced at intervals of 2 to 3 hours during the day, the patient was considerably improved. He began soon, however, to relapse. To counteract his increasing symptoms, his intake of neostigmine bromide was raised to 16 tablets a day, augmented by intramuscular injections of neostigmine methylsulfate, 1 mg. each, 6 times a day. His average dosage before entering the hospital was 2 tablets of neostigmine bromide every 2 hours during the daytime, and every 3 hours at night. With each dose he took 4 drops of tincture of belladonna to prevent a diarrhea which occurred without it, using about 44 drops in each 24 hours. He swallowed only liquids with difficulty, being unable to take any solid food. A loss of 20 pounds in weight had occurred during the past 6 months. The response to the above dosage was irregular. The disease progressed slowly by relapses and mild remissions, with a general downward course. Up to a week before admission the patient was able to walk with only moderate weakness. During the following week he collapsed rapidly. Except for the symptoms noted above, the patient had few complaints. There was some dyspnea on exertion, a tendency towards mucus formation in his throat with an annoying cough and moderate urgency and frequency of urination. His mood was one of coöperativeness, without undue depression.

Past History. The patient had served as a missionary in India from 1901 to 1940, where he had several attacks of malaria. His last chill occurred in July, 1942, this attack being relieved by quinine, as in the past. There was also a history during his years in India of frequent intestinal upsets, with mild to severe diarrhea. Peptic ulcers were relieved by diet, without operation, in 1936.

Some dribbling at the end of urination had been noted for 10 years, with considerable frequency in the last few years. In October, 1941, obstruction to urination occurred. The prostate gland was removed by perineal prostaticectomy at the Massachusetts General Hospital in November, 1941, and a papillary tumor from the bladder by transurethral resection in July, 1942, both operations taking place before the onset of his present symptoms of myasthenia gravis. Pathologic examination of the tumor showed it to be a carcinoma, Grade 2A.

Physical Examination. On admission, May 21, 1943, the patient was gravely ill. His eyes were fixed in about the midline, with moderate ptosis. The jaw hung partly open and the facial muscles were nearly immobile. His head could not be raised from the bed. Speech was thick, but understandable; his tongue could only be protruded to the line of the teeth. The arms could not be lifted above the level of the shoulders. The patient could move his legs, but could not turn over in bed. Swallowing was limited to small amounts of liquids. Choking spells occurred a number of times each day, often with shallow, diaphragmatic, gasping respiration. His throat was nearly constantly filled with thick mucus.

The patient's heart was slightly enlarged and the sounds were of poor quality. The blood pressure was 140 systolic, 100 diastolic. The general physical examination was otherwise not remarkable, except for coarse râles throughout both lungs.

Laboratory Reports. The specific gravity of the urine was normal; occasionally a trace of albumin was present, with a rare hyaline or granular cast. The hemoglobin was 15.3 gm. per 100 cc. The W.B.C. count was 4900 per c.mm., the differential count being within the limits of normal. The R.B.C. and platelets appeared normal; no malarial parasites were seen. The stool showed no blood, parasites or ova. Lumbar puncture was not done.

Treatment. On entrance to the hospital it was impossible for the patient to swallow neostigmine bromide by mouth and parenteral medication was begun (Fig. 1). At first 1 mg. of neostigmine methylsulfate was injected intramuscularly every 2 or 3 hours. As this dosage was insufficient to prevent attacks of dyspnea, the dosage was gradually increased to hourly injections throughout the 24 hours of 1 mg. or 1.5 mg. each. On one day he received

	1943	7	8	9	10	11	12N	1	2	3	4	5	6	7	8	9	10	11	12M	1	2	3	4	5	6	Mg.	
May 23	00		00		00						00			00			00		00		00		00		00	11.0	
24		00		00					00	0		00	00	00		00		00	00	00		00		00		12.5	
25		00		00		00	*	00			00		00		00		00		00		00		00		00	12.0	
26		00		00		00	*	00			00	00	00		00	00	00	00	00		00		00		00	15.0	
27	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	24.0	
28	00	00	00	00	00	00	00	00	00	00	000	000	00	00	00	00	00	00	00	00	00	00	00	00	00	25.0	
29	00	00	00	00	00	00	00	00	00	00	000	000	000	00	00	00	00	00	00	00	00	00	00	00	00	25.5	
30	00	00	00	00	00	00	00	00	00	00	000	000	000	000	000	00	00	000	00		00	00	00	00	00	26.5	
31	00	00	00	00	000	*	00	00	000	00	00	00	00	00	00	00		000			000					22.0	
June 1	00	00	000	000	000	000	000	00	00	000	000	000	000	000	000	000	000		00	00	00	00	00	00	00	31.0	
2	00	00	00	00	00	00	00	00	000	*		000	000	000	000	000	000	000	00	00	00	00	00	00	00	28.5	
3	00	00	00	000	*		00	000	000	000	000	000	000	000	000	000	000	000	00	00	00	00	00	00	00	28.0	
4	00	00	00	00	00	000	*	00	00	000	000	000	000	000	000	000	000	000	00	00	00	00	00	00	00	28.5	
5	00	00	00	00	000	*	00	00	000	000	000	000	000	000	000	000	000	000	00	00	00	00	00	00	00	29.0	
6	00	00	00	00	00	000	*	000	000		00	000	000	000	000	000	000	000	00	00	00	00	00	00	00	27.5	
7	00	00	00	00	00	000	*	000	000		00	000	000	000	000	000	000	000	00	00	00	00	00	00	00	27.5	
8	00	00	00	00	000	*	000	00	00	000	000	000	000	000	000	000	000	000	00	00	00	00	00	00	00	27.5	
9	00	00	00	00	00	000	*	000	000		00	000	000	000	000	000	000	000	00	00	00	00	00	00	00	28.5	
10	00	00	00	00	000	*	000	00	00	000	000	000	000	000	000	000	000	000	00	00	00	00	00	00	00	28.5	
11	00	00	00	00	00	000	*	000	000		00	000	000	000	000	000	000	000	00	00	00	00	00	00	00	28.5	
12	00	00	00	00	000	*	000		00	000	000	000	000	000	000	000	000	000	00	00	00	00	00	00	00	26.5	
13	00	00	00	00	000	*	000		00	000	000	000	000	000	000	000	000	000	00	00	00	00	00	00	00	26.5	
14	00	00	00	00	00	00	00	00	00	+	000	+	000	+	000	+	000	+	00	00	00	00	00	00	00	211 (75.0)	
15	00	+	00	+	00	+	00	+	00	+	00	+	000	+	000	+	000	+	00	00	00	+	00	00	00	+	15.5 (150.0)
16	00	+	00	+	00	+	00	+	00	+	00	+	000	+	000	+	000	+	00	00	00	+	00	00	+	00	15.5 (150.0)
17	+	00	+	00	+	00	+	00	+	00	+	000	+	000	+	000	+	000	+	00	00	+	00	00	+	00	15.0 (165.0)
18	+	00	+	00	+	00	+	00	+	00	+	000	+	000	+	000	+	000	+	00	00	+	00	+	00	+	14.0 (180.0)
9	+	00	+	00	+	00	+	00	+	00	+	000	+	000	+	000	+	000	+	00	00	+	00	+	00	+	14.0 (140.0)

Fig. 1.—The hourly intake of neostigmine methylsulfate and neostigmine bromide in a severe case of myasthenia gravis during the first 3 weeks of treatment. The chart is divided into 3, 8-hour daily periods, according to the nursing schedule. 0 = neostigmine methylsulfate, 0.5 mg. (1-2000). + = neostigmine bromide, 15 mg. An asterisk denotes intravenous medication. The total intake in milligrams of each drug is given in the right-hand column, the amount of the neostigmine bromide being in parenthesis.

31 mg. of neostigmine methylsulfate. Three mg. of this total each day was given intravenously in 1500 cc. of glucose solution to which it was added. The 5% glucose solution was also reinforced by 100 mg. of vitamin C, 10 mg. of thiamine chloride, 100 mg. of nicotinamide and 10 mg. of riboflavin. The formula of intravenous medication was slightly changed from time to time, but remained relatively constant for 3 weeks; the rate of flow was about 70

drops per minute. No difficulties were encountered in using this daily intravenous therapy.

The patient became well adjusted to his schedule of neostigmine in about a week and was maintained on 26.5 mg. to 29 mg. of neostigmine methylsulfate every 24 hours for the next 2 weeks. He showed no acquired tolerance to

		AM					PM					AM					Mg.												
		7	8	9	10	11	12N	1	2	3	4	5	6	7	8	9		10	11	12M	1	2	3	4	5	6			
June	20	+	00	+	00	+	00	+	00	+	000	+	000	+	000	+	000	+	00	+	00	+	00	+	00	14.0 (180.0)			
	21	+	00	+	00	+	00	+	00	+	000	+	000	+	000	+	000	+	00	+	00	+	00	+	00	14.0 (180.0)			
	22	+	00	+	00	+	00	+	00	+	000	+	000	+	000	+	000	+	00	+	00	+	00	+	00	14.0 (180.0)			
	23	+	00	+	00	+	00	+	00	+	000	+	000	+	000	+	000	+	00	+	00	+	00	+	00	14.0 (180.0)			
	24	+	00	+	00	+	00	+	00	+	000	+	000	+	00	+	000	+	00	+	00	+	00	+	00	13.5 (180.0)			
	25	+	00	+	00	+	00	+	00	+	000	+	000	+	00	+	000	+	00	+	00	+	00	+	00	13.0 (180.0)			
	26	+	00	+	00	+	00	+	00	+	000	+	000	+	00	+	000	+	00	+	00	+	00	+	00	13.0 (180.0)			
	27	+	00	+	00	+	00	+	00	+	000	+	000	+	00	+	000	+	++		++		++		++	9.0 (240.0)			
	28	+	00	+	00	+	00	+	00	+	000	+	000	+	000	+	00	++		++		++		++		++	9.5 (240.0)		
	29	+	00	+	00	+	00	+	00	+	000	+	000	+	00	+	000	++		++		++		++		++	9.5 (240.0)		
30	+	00	+	00	+	00	+	00	+	000	+	000	+	00	+	00	++		++		++		++		++	9.0 (240.0)			
July	1	+	00	+	00	+	00	+	00	+	000	+	000	+	00	+	00	++		++		++		++		++	9.0 (240.0)		
	2	++		++		++		++	0	+	000	+	000	+	00	+	00	++		++		++		++		++	5.5 (300.0)		
	3		++		++		++	++	+	000	+	000	+	00	+	00	+	++		++		++		++		++	5.0 (350.0)		
	4		++		++		++	++	+	000	+	000	+	00	+	00	+	++		++		++		++		++	5.0 (350.0)		
	5		++		++		++	++	+	000	+	000	+	00	+	00	+	++		++		++		++		++	5.0 (350.0)		
	6		++		++		++	+	++	+	000	+	000	+	00	+	00	+	++		++		++		++		++	5.0 (330.0)	
	7		++		++		++	+	++	+	000	+	000	+	00	+	00	+	++		++		++		++		++	5.0 (330.0)	
	8		++		++		++	+	++	+	000	+	000	+	00	+	00	+	++		++		++		++		++	5.0 (330.0)	
	9		++		++		++	+	++	+	000	+	000	+	00	+	00	+	++		++		++		++		++	5.0 (330.0)	
	10	+	++	+	++	+	++	+	++	+	000	+	000	+	00	+	00	+	++		++		++		++		++	5.0 (375.0)	
	11	+	++	+	++	+	++	+	++	+	++	++	++	+	+	+	+	+	++		++		++		++		++	480.0	
	12	+	++	+	++	+	++	+	++	+	++	++	++	+	+	+	+	+	++		++		++		++		++	495.0	
	13	+	++	+	++	+	++	+	++	+	++	++	++	+	+	+	+	+	++		++		++		++		++	1.0 (480.0)	
	14	+	++	+	++	+	++	+	++	+	++	++	++	++	++	++	++	+	+	++		++		++		++		++	1.0 (525.0)
	15	+	++	+	++	+	++	+	++	+	++	++	++	++	++	++	++	+	+	++		++		++		++		++	1.0 (500.0)
	16	+	++	+	++	+	++	+	++	+	++	++	++	++	++	++	++	+	+	++		++		++		++		++	1.0 (500.0)
	17	+	++	+	++	+	++	+	++	+	++	++	++	++	++	++	++	+	+	++		++		++		++		++	1.0 (500.0)

FIG. 2.—The hourly intake of neostigmine methylsulfate and neostigmine bromide in a severe case of myasthenia gravis during the second 3 weeks of treatment. For an explanation of the symbols used, see the legend under Figure 1.

the drug and intestinal stimulation was minimal. There were few cramps, but he had only 2 to 4 soft bowel movements each day without diarrhea. Atropine sulfate, 0.6 mg., was given only 5 times in 8 weeks. On the other days a few drops of tincture of belladonna was used. As his general condition slowly improved, swallowing became possible. Three weeks after entrance to the hospital (Fig. 1) the intravenous medication was stopped and administration of neostigmine bromide orally was slowly substituted for some of the intramuscular and intravenous injections (Fig. 2). Over a period of the next 5

weeks, treatment by mouth was gradually extended, until at the end of 8 weeks the patient was maintained on oral neostigmine bromide, as he had been 3 months before entering the hospital (Fig. 3). Ephedrine sulfate, 24 mg.,

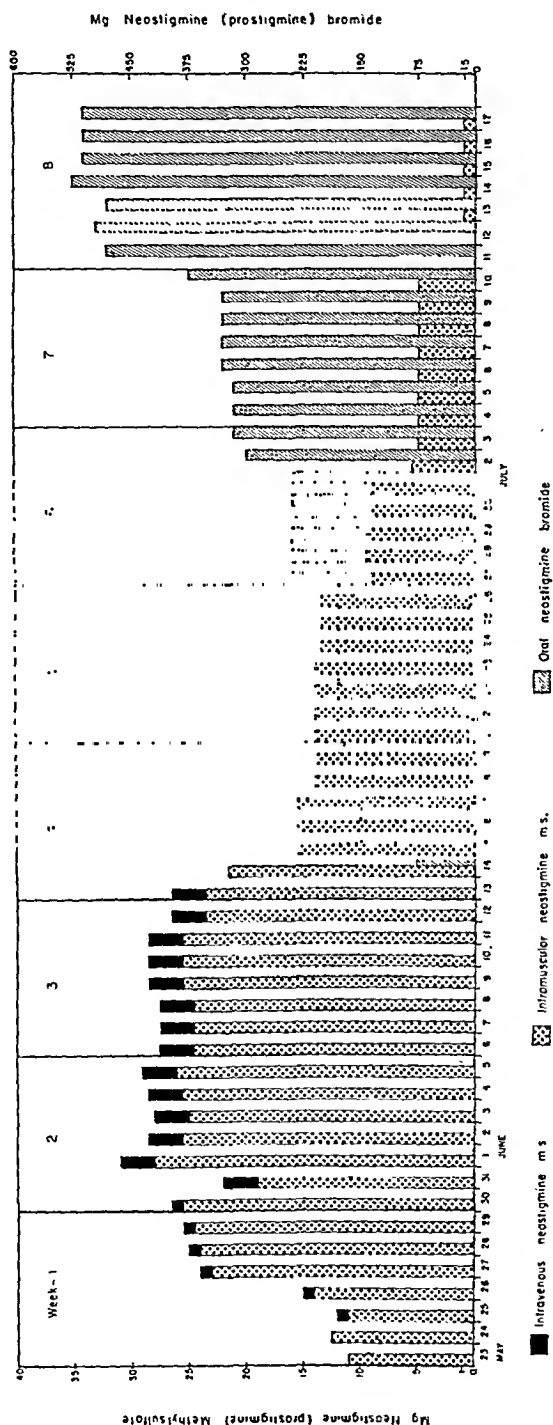


FIG. 3.—The total intake of neostigmine methylsulfate and neostigmine bromide over a period of 6 weeks in a severe case of myasthenia gravis. The amount of neostigmine methylsulfate given each day may be measured in milligrams by the scale in the left-hand column. The scale in the right-hand column is for measuring in milligrams the daily intake of neostigmine bromide. As the patient regained the power of swallowing, a gradual shift to oral medication may be noted.

1 tablet, crushed in water, 4 times a day, was used for about 4 weeks, but was discontinued because of restlessness and insomnia. Otherwise the only medication for myasthenia gravis used was neostigmine. Tincture of digitalis,

10 drops in water, once a day, was given throughout the patient's stay of 8 weeks in the hospital. On 2 occasions, when cardiac failure threatened, 4 cc. (0.8 mg.) of cedilamide was given and on another, 1.5 cc. of coramine, intravenously.

Nursing and Feeding. Of most importance was the constant nursing care; 3 nurses, each on 8-hour duty were employed to ensure constant observation. Thick, tenacious mucus was removed from the mouth and throat by suction or by postural drainage. The hourly medications required much of the nurses' time. The opening of 60 or more ampules a day was a task, finally obviated when neostigmine methylsulfate was procured in ampules of 10 cc., each containing 5 mg.*

During the first week of hospitalization the patient was only able to swallow a small amount of liquid. On some days 500 to 1000 calories of food could be given by mouth; this was supplemented by 200 to 400 calories of glucose, intravenously. Because of the danger inherent, when dysphagia is present, to intubation in myasthenia gravis, tube-feeding was not resorted to. As the patient slowly improved, due to better adjustment of his intake of neostigmine methylsulfate, his total calorie intake during the second week was raised to a level of 1000 calories a day. Gradually this was pushed up to a level of over 2000 calories before the patient left the hospital at the end of 8 weeks. Most of the food consisted of milk, cream, puréed vegetables, eggs, finely ground-up meat, and bread. On the day he left the hospital, July 30, 1943, about 2400 calories were taken by mouth.

Subsequent Course. The patient did not do well at home. Special nursing could not be provided and adequate medical supervision was not available. He died of respiratory failure, or possibly of cardiac complications, August 6, 1943, a week after discharge. Postmortem examination was not allowed.

Discussion. The use of neostigmine in the treatment of myasthenia gravis is based upon the following assumptions: (1) acetylcholine is a necessary ingredient in the complex chemical status that permits the passage of an impulse from nerve to muscle; (2) cholinesterase is the enzyme concerned with the destruction of acetylcholine by hydrolysis; (3) in myasthenia gravis there is an abnormal reaction at the myoneural junction between acetylcholine and cholinesterase; (4) neostigmine is a potent inhibitor of cholinesterase activity, combining loosely with it; (5) when neostigmine is dialyzed off from cholinesterase *in vitro*, restoration of full enzymatic activity results; (6) probably a similar chemical reaction takes place *in vivo*, unless a sufficient supply of neostigmine is continuously at hand to inhibit cholinesterase activity.

Thus the therapeutic aim in the treatment of myasthenia gravis is to supply enough neostigmine to a patient to offset the activity of the cholinesterase, resulting in an excessive or too rapid destruction of the acetylcholine. Cholinesterase may be found along the nerve pathways, at the level of the nerve cells in the central nervous system and at the myoneural junction. In myasthenia gravis, the main focal point of imbalance appears to be at the myoneural junction, but other points may also be involved. With our present knowledge, a chemical imbalance at the myoneural junction accounts best for the main symptom of the disease, namely excessive fatigue of muscular response to voluntary nerve stimulation.

* These special ampules were provided by Hoffmann-La Roche, Inc., for the purpose of clinical research.

When oral treatment is given, using prostigmine bromide, there are many factors that tend to prevent a continuous and even supply reaching the myoneural junction of the affected muscles. In order to maintain the highest and steadiest level of neostigmine at the focal point, the drug is given in spaced doses during the day and night; larger doses are used at times of greatest fatigue, as in the afternoon period and during mealtime. Too rapid removal from the stomach is avoided by an ingestion of some food with each oral medication, or the drug may be absorbed sublingually. Parenteral treatment may be used to augment the oral intake in times of excessive need. Thus a carefully planned, schedule dosage is sufficient control for the maintenance of the average case of myasthenia gravis. The uncontrolled factors, such as the failure to assimilate the drug, its loss in other areas of the body than the specific myoneural junctions involved and the destruction and elimination of neostigmine without absorption, a matter not fully understood, are not of great clinical importance in the treatment of most cases. Such unknowns can be offset by increased dosage and large doses do not appear to affect most patients adversely.

With the use of neostigmine parenterally, the problem becomes less complex, for the uncertainty of absorption *via* the gastro-intestinal tract in oral medication, is eliminated. The principle of treatment remains unchanged. Maintenance is established at an adequate level, although, as indicated in the case abstract, the level may exceed our preconceived ideas in regard to toxicity and tolerance. When the patient, reported upon, was doing badly, in the first few days of his hospitalization, it was soon discovered that underdosage and not overdosage was the fault. The daily intake of 11 mg. was raised to nearly 3 times that amount and the patient became well adjusted and nearly symptom free. At the proper time, moreover, when he was fully maintained and improved, the amount of the drug was reduced without ill effect and oral medication was substituted. No tolerance developed. This has been found to be so in most cases of myasthenia gravis treated by the author. What is usually called "developing a tolerance to the drug" is merely an acknowledgment of inadequate dosage.

The intravenous use of neostigmine methylsulfate was first tried in this case. It was found that the drug was well tolerated, that it could be added to glucose solution and other forms of medication could be used in the same intravenous preparation. When given over a period of hours, the same amount could be used as was given intramuscularly. Using the drip method, 1.5 mg. could be given in 1 hour. Subsequently, in other patients this dose has been doubled, without ill effects. The possibility of using neostigmine intravenously opens up a new field for emergency treatment and, since experience with this patient, the drug has been frequently used for this purpose. No difficulties have been encountered. On the basis of experiments with the related drug, physostigmine,⁴ neostigmine has been given by continuous intravenous infusion in myasthenic patients in the Department of Surgery at the Massachusetts General Hospital.⁴ By this means the neostigmine needs of the individual patient were assayed preoperatively and appro-

priate levels of cholinesterase inhibition were maintained during and after thymectomy.

The signs in man of a fatal dosage of neostigmine are uncertain. No patient is known to have died of the drug. When patients are taking more neostigmine than is needed to inhibit the cholinesterase, muscular fibrillations or fasciculations will appear as evidence of cholinergic overstimulation of the muscular skeletal system. In addition, salivation, a lowering of the heart rate and a stimulation of peristaltic activity, with or without cramps, will be noted. These are the signs that occur when the drug is given to a normal person,³ and they are seen in cases of myasthenia gravis if more neostigmine is given than is needed. When large doses are used, these signs should be watched for. In our experience, the most important early sign is the fibrillation or fasciculation of the facial muscles. The symptoms of overdosage usually respond to atropine sulfate.

Summary. 1. Patients with severe myasthenia gravis may be maintained on neostigmine methylsulfate, intramuscularly, spaced at hourly intervals, in doses up to 31 mg. per 24 hours.

2. The drug may also be given intravenously, in doses as high as 3 mg. per hour, by the continuous drip method.

3. Neostigmine and other drugs can be safely added to the intravenous glucose solution.

4. Tolerance for neostigmine was not shown in the doses used.

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PURULENT MENINGOCOCCAL ARTHRITIS

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ARTHRALGIA and myalgia are common complaints at the onset of many of the acute febrile diseases and meningococcal infections are not exceptions in this regard. Most authors on the subject of meningo-

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coccal infections mention the frequency with which joint and muscle pains occur but few give any particulars concerning the joint manifestations. When arthritis is referred to it is usually described as accompanying the rash and disappearing with the rash without any treatment being needed and without leaving any sequelæ. Indeed, this form of arthritis has been regarded as so mild that little notice has been given to it. Apart from this transient form of arthritis purulent meningococcal arthritis occasionally occurs.

At the present time, when sulfonamide drugs are so effectively being used in the treatment of meningococcal infections, the septicemic stage of the disease is readily controlled, so that we may expect to see fewer of the metastatic manifestations than ever before. But it is of interest that, even before the day of sulfonamides, arthritic manifestations of meningococcal infections had been noted; but, nevertheless, there have been few reports of purulent meningococcal arthritis. The first observers of "spotted fever" have given us excellent clinical descriptions of the disease, and their remarks about arthritis are pertinent. North and Swords²² called attention to the "rheumatism" in connection with cerebrospinal fever, and Welch, Jackson and Warren⁴¹ said: "In some cases swellings have occurred in the joints and limbs. These have been very sore to the touch and their appearance has been compared to that of gout. The parts feel as if they had been bruised. These swellings are in the smaller as well as the larger joints and are often of a purple color. Those of the small joints especially soon disappear as the disease approaches its crisis." This description was made before the discovery of the meningococcus as the cause of "spotted fever" and it very nicely dovetails with the word-picture given to us by Herrick and Parkhurst¹² at a later date.

von Fronz,³⁸ in 1897, first isolated the meningococcus from fluid drawn from a joint and should be credited with the first case of proven meningococcal arthritis. In 1899, Gwyn,⁸ working on Osler's service at Johns Hopkins Hospital, isolated the meningococcus from the blood, "joint fluid and cerebrospinal fluid of a case which Osler described as illustrating probably the maximum degree of involvement of the joints in cerebrospinal fever." There was "swelling and redness of both elbows, the right wrist, the right knee, and several of the smaller joints of the hands."

It was the violence of the polyarthritis noted in the case here reported that attracted our attention to the subject of meningococcal arthritis, and we believe that it also represents "the maximum degree of involvement of the joints in cerebrospinal fever."

Case Reports. CASE 1. E. D. E. (A18900), age 52, white, widowed. This saleswoman was in her usual good health until February, 1943, when she suffered from a "cold" with cough, sore throat, and aching all over. Her physician prescribed white pills to be taken ever 4 hours (not sulfonamide medication). After a week in bed and several days spent about the house, the patient felt sufficiently well to return to her work, but felt only "fairly well," for she still had chilly sensations and muscular aching.

January 10, 1943: Sore throat, malaise, headache, general muscular aching and nausea were noted; the same physician prescribed the same tablets once

again. Only 3 doses of the medicine had been taken when nausea and vomiting began. General aching became more severe, joint pains were complained of, and finally chills began. These chills were "shaking chills" and after the first one "spots" appeared on the hands, feet, forearms and lower legs. The patient ascribed her nausea to the medication and took only 7 tablets in all. The repeated chills, high fever, headache and exquisitely tender joints finally forced the patient to come to the hospital.

January 15, 1943: The patient was acutely ill and complained bitterly of the pain in "every joint;" she was mentally clear but was in such pain that both the history and examination were abbreviated. Temperature was 103° F., pulse 110, and respirations 25, blood pressure 150/70. The skin presented a fine, purpuric rash over the ankles and lower thirds of both legs, and in addition several petechiæ on the thighs and abdomen. Also, there were scattered over both hands, forearms and feet several larger purpuric spots which measured from 3 to 10 mm. in diameter. None of these "spots" blanched on pressure, and several of the larger ones were indurated and tender; the likeness to erythema nodosum was noted. The thorax, back and abdomen showed only a few scattered petechiæ.

The eyes presented a purulent discharge which was crusted on the eyelashes and eyelids so as to almost glue the lids together. The corneæ were clear and there were no ulcerations.

The chest was clear, the heart regular and apparently normal, and the abdomen soft. A special effort was made to feel the spleen, but it could not be palpated.

All joints were exceedingly painful, the patient refused to make any effort to move them and the slightest passive movement caused pain. Both hands looked frankly edematous, the dorsum of each being swollen and tense. The resemblance to the infections of the hand was striking. There was a splotch of purple discoloration over each of the metacarpophalangeal joints and the dull-red of inflammation about both wrists; the wrists were swollen, the right more than the left, and the patient would tolerate no movements of either hand. Both elbows were tender, swollen and red, and held in semiflexion across the abdomen. Due to the pain in the lower arms, the shoulders could not be properly evaluated, tenderness on palpation was elicited but there was no swelling and no redness. The neck was supple, the temporomandibular joint normal, and the chest gave no pain on forced inspiration and expiration. Both feet were swollen and both ankles were red, hot and tender; movement of the toes was painful. The left ankle joint was larger than the right, but both presented evidence of effusion into the joints. Both knees were swollen, hot, red and tender and fluid was present in both joints. Movements of the hips were not tested.

The arthritis in this case was the most striking feature and, in view of the ophthalmia, the joint symptoms, and a rather indefinite social history, the diagnosis of gonococcemia and gonococcal arthritis was entertained. The patient vigorously denied exposure, urethral and cervical smears were negative for gram-negative diplococci, and an unsatisfactory pelvic examination showed nothing abnormal.

Meningococcemia was suspected, although none of us had ever seen such an outspoken and acute arthritis in this condition. Lumbar puncture yielded clear spinal fluid under normal pressure, the cell count was normal, no organisms were demonstrated on smear, and culture of this fluid was later reported as negative.

The purpuric nature of the skin rash, together with knowledge of previous medication, suggested a blood dyscrasia. Tests of capillary fragility gave normal results, bleeding time 2 minutes 5 seconds, clotting time 4 minutes, prothrombin time (Quick) 16 seconds, clot retraction at the end of 1 hour, platelet count 429,000 per c.mm. were all normal values.

The fulminating nature of the arthritis and the fine rash chiefly on the lower extremities caused us to think of Haverhill fever. Dr. L. E. Sutton²⁵ saw this

case in consultation and agreed that the clinical appearance of this patient was such as to justify the consideration of this diagnosis.

Aspiration of the left knee was done and approximately 50 cc. of thick, yellow pus was obtained; a smear of this pus revealed countless numbers of both intracellular and extracellular gram-negative diplococci. Fluid was obviously present in both ankles, certainly in the right wrist, and probably in several of the metacarpophalangeal joints, but it was deemed unwise to tap these joints for purely academic reasons.

The patient was given 6 gm. of sodium sulfadiazine intravenously and 1 gm. orally every 4 hours thereafter. Morphine was given without stint for the relief of joint pain, and splints were applied to the left leg, the right leg, and the right wrist. These measures made the patient fairly comfortable.

As late as the 5th hospital day it was the general feeling that this woman suffered from gonococcemia and gonococcal arthritis; this feeling had been strengthened by the reporting of a positive gonococcal complement-fixation test. But at this time both the blood culture and the culture made from the joint fluid were reported as showing growths of meningococci. The organism was typed as a Type I meningococcus by the National Institute of Health. The gonococcal complement-fixation test was repeated and found positive on 2 more occasions.

The fever subsided by lysis, the joints became progressively less tender and swollen, and the rash rapidly faded. The larger purpuric spots left brownish discolorations and some of the "erythema-nodosum-like" lesions during their period of regression took on the appearance of bruises with all of the attendant color changes.

Sulfadiazine therapy was given for 19 days at which time the patient had a total white count of 3200 and was running a mild fever; the drug was discontinued. Most of the joints had become non-painful, but the left knee was still swollen, and the right hand was still definitely swollen. The knee could be flexed beyond 90 degrees but it felt "stiff." Grasp with the right hand was poor and the wrist could not be dorsiflexed.

February 21, 1943 (30th hospital day): Without apparent cause the patient became fretful, recalcitrant, resisted the medical attendants and talked foolishly. During the following days the patient became actively hallucinated, expressed fears that the nurses and doctors were poisoning her, and became unmanageable on an open Medical Ward. On the 49th hospital day this woman was discharged in the care of her family. There is no explanation for this psychosis.

Follow-up of this patient revealed that on the 80th day from the onset of her arthritis the left knee still ached, the left ankle swelled after walking, the right hand remained swollen. Roentgen ray of the right wrist revealed "destruction and narrowing of the joint space due to infectious arthritis."

CASE 2. Miss L. B., age 24 years, white, single. This case-worker had for several months been employed in social work and had been visiting in numerous homes. While visiting her sister, she was taken ill with a "cold," headache, muscle soreness and a rash. The sister, a student nurse, put the patient to bed and went off to attend a lecture, the subject of which was "Meningococcemia and Meningococcal Arthritis," which was being presented by the author before the Staff of the Medical College of Virginia. Returning from the lecture, this observant student nurse had her sister admitted to the hospital at once with the presumptive diagnosis of meningococcal infection, and the author was called to see the case.

The patient was alert and somewhat bewildered that she should be so precipitously admitted to the hospital. Examination revealed a temperature of 102° F., pulse 100, respirations 24. The patient was comfortable, complained of slight soreness of the muscles generally, slight headache and some slight nausea. The neck was slightly painful on anterior flexion, Kernig's sign was negative bilaterally, and the reflexes were physiologic. The skin presented a hemorrhagic rash limited to the arms and legs, both palms and soles presented spots ranging from 5 to 10 mm. in diameter. The chest was clear, the heart normal in size, rhythm and sounds, the abdomen was soft, and the spleen

could not be felt. A lumbar puncture was done and slightly cloudy fluid was obtained that revealed 500 cells per c.mm.; organisms were not seen on smear but culture of this fluid was positive for meningococci. A blood culture taken at this time was noted to be positive for meningococci.

The joints were carefully examined and the left knee was found to be slightly swollen. The patient herself had not been aware of this fact and there was no pain on manipulation of the joint, flexion was slightly limited by a feeling of "fullness." There was no redness or tenderness of this joint. Aspiration was done and thick, yellowish fluid was obtained which on smear revealed gram-negative diplococci. Culture of this fluid was positive for meningococci.

The patient was given 3 gm. of sulfadiazine as an initial dose and 1 gm. every 4 hours to a total of 25 gm. Recovery was entirely uneventful, no special treatment was given to the knee, and normal function was restored. Follow-up 1 year later revealed that there had been no disability with regard to the left knee.

Discussion. It is difficult to know the exact incidence of meningococcal arthritis, for many authors either do not mention it at all or mention it so slightly that one wonders whether they refer merely to arthralgia or to true arthritis. When arthritis is specified, it is frequently stated that it is transitory, disappears with the rash which accompanies it, and does not present the local signs of inflammation.^{5,19,27,30} The statement is made almost universally that meningococcal arthritis is "self-limited," that little or no treatment is necessary, and that restoration of joint function is complete. It is small wonder that little attention has been paid to meningococcal arthritis.

Herrick and Parkhurst¹² collected the largest single series of cases of meningococcal arthritis and classified the different forms that the disease might take. Their Type C was merely the arthritis of serum sickness and needs no further comment. Of Type A they said, "Almost all these cases have profuse hemorrhagic rashes coincident with the polyarthritis. In many but not in all instances, the arthritis is transitory as the rash. It would seem that these early joint symptoms are due to hemorrhage into the articular and periarticular structures, especially the synovia, and are identical with the hemorrhagic lesions of the skin and serous membranes." Bauer and Short¹ similarly explain arthritis as "hemorrhage into the joints," but it is of interest to note that Herrick and Parkhurst¹² clearly stated that aspiration was not done in any of these cases, so that no evidence is offered as proof of "hemorrhage into the joints." However, Keefer *et al.*¹⁷ studied several joints pathologically and demonstrated acute inflammatory changes and gram-negative diplococci in the deep layers of the synovia, but an intact synovial surface layer, thus establishing the fact that the process may be purely a "synovitis." These authors concluded, "Meningococcic arthritis is a metastatic lesion involving first the deeper synovial tissues. Later, infection invades the superficial cells with effusion of fluid into the joint cavity and varying degrees of destruction of the cartilage. It is essentially a metastatic acute synovitis."

Thus the Type A arthritis of Herrick and Parkhurst can be designated as an acute synovitis. As the result of extension of the synovitis, Type B arthritis may result. "With few exceptions only one joint is

affected, generally the knee, occasionally the ankle, hip, shoulder, wrist or elbow. . . . Effusion is a prominent feature so that aspiration of the synovial capsule is suggested in many cases. Swelling is great, but redness, pain, tenderness and limitation of motion are surprisingly slight. Often a tensely swollen joint can be manipulated freely, with only moderate discomfort. In no other acute arthritis is there this striking disproportion between the swelling and the other inflammatory signs. . . . The duration of the process is usually from 1 to 4 weeks, recovery being gradual but complete. Rarely stiffness and slight pain or muscular spasm remain for a long time."

TABLE 1.—REPORTED CASES OF MENINGOCOCCAL ARTHRITIS

Reference	No. of cases meningococcus infection	No. of cases with joint effusions specifically	Cases with "arthritis" (%)
Rogers*	Not stated	Not stated	20.0
Osler*	21	Not stated	9.5
Councilman, Mallory, Wright*	111	Not stated	5.4
Sophian ³²	Not stated	Not stated	10-15
Rolleston and Andrewes ²⁹	1773	Not stated	5.3†
Hodes and Strong ¹³	110	Not stated	4.5
Rundlett, Gnassi, Price ³⁰	17	Not stated	41.0
Stone, Truitt ³⁴	215	1	24.0
Herrick ¹¹	315	Not stated	10.0
Stott, Copeman ³⁵	17	3	17.6
Harries ⁹	500	Not stated	5.4
Joe ¹⁵	500	Not stated	4.2
Lepper, Sweet, Dowling ²⁰	121	Not stated	2.4
Thomas ³⁷	1935	Not stated	"a few"
Waghelstein ³⁹	580	Not stated	2.7
Tillett, Brown ²⁶	26	Not stated	43.0
Boger, Robertson†	125	2	3.6

* Cited by Herrick and Parkhurst.¹²

† Synovitis.

‡ Unpublished data.

Certainly this type of joint disease deserves the name of "purulent arthritis," and it is to this type of meningococcal arthritis that we wish to direct attention. Case 2 beautifully illustrates the painlessness and the absence of local manifestations of inflammation in this type of joint involvement.

Case 1 stands in sharp contrast to Case 2. It seems likely that the patient had been ill for a month or more and that her recurrent muscle aches and chilly sensations were due to a chronic meningococcemia. At the time of hospitalization the meningococcal septicemia was at its height, with the production of a marked purpuric rash and a very acute polyarthritis; the coincidence of these two manifestations must be stressed. This polyarthritis was probably due to acute synovitis, and most of the lesions producing the joint manifestations resolved in a short time; but a number of the joints at this time were noted to have frank effusions in them. The evolution of this case shows rather clearly the relationship of Type A and Type B arthritis, the latter being merely an extension of the former, and the clinical observations in this case coincide exactly with the pathologic studies of Keefer *et al.*¹⁷

The coincidence of the rash and arthritis has been repeatedly noted, and those cases of chronic meningococcemia in which recurrent septi-

cemia with the production of chills and fever, rash and arthritis permits repeated observations of the same sequence of events, seem to establish a close relationship between the two phenomena. There seems little reason to doubt that the synovial linings of joints present a "rash" just as the skin does, with resultant arthritic symptoms, but it still seems unnecessary to postulate hemorrhages into the joints. On the skin the meningococcal rash may present macules, petechiæ, intracutaneous hemorrhages and erythema nodosum-like lesions; and if one grants the same variability of the rash on the synovial surfaces, one can readily understand pain, tenderness, redness and "arthritis as transient as the rash which accompanies it,"^{12,41} without postulating hemorrhage into the joint.

If we regard the profuseness of the skin rash as a possible indication of a similarly profuse involvement of synovial surface, it becomes merely a quantitative relationship between profuseness of the rash and the extent of the synovial lining of a particular joint, which determines the frequency with which the joint is involved by a purulent effusion. The larger the extent of the synovial lining of a particular joint the more likely it is that one or more of the septic metastases will extend into the joint. This seems to be compatible with the finding that the larger joints, and particularly the knee, are most often involved by suppurative meningococcal arthritis.

Despite the commonness of meningococcal infections and the naming of the disease "spotted fever" because of the commonness of the rash, purulent meningococcal arthritis is a relatively rare disease. Table 1 presents some scattered statistics on the incidence of arthritis in the presence of meningitis, but none of the authors cited presents bacteriologic proof of any case of arthritis noted. Herrick and Parkhurst¹² collected 16 cases of Type B arthritis; only 8 were aspirated and in only 4 was the meningococcus isolated. Schein³ found 23 cases of "meningococcal arthritis" during a 10-year period, but only 4 of these cases were established bacteriologically. Kobayoshi,¹⁸ Gwyn,⁸ Jaffe¹⁴ each proved 1 case by isolation of the meningococcus from joint fluid. Dock,⁶ in reviewing 68 cases of meningococcemia, mentions 3 joint effusions but gives no bibliography. Rolleston²⁸ mentions aspiration of a joint, but no culture was obtained; similarly, Stott and Copeman³⁵ encountered 3 joint effusions, but no aspirations were done. Moss²¹ reported 1 case with bilateral effusions of the knees and another case with a joint effusion, but cultures were sterile. Although we have not reviewed the literature exhaustively, it seems plain that the isolation of meningococci from the joints is uncommon.

In the light of the close relationship between the rash and arthritis, and the fact that both are manifestations of septicemia, the demonstration of meningococci in the blood or cerebrospinal fluid might appear to be proof of etiology of the joint manifestations. While such evidence is probably acceptable we believe that anything short of the demonstration of meningococcus from the joint involved leaves the case open to question. Cattell^{3a} calling attention to the rarity of meningococcal arthritis, nevertheless fails to present bacteriologic

proof of his case. It may seem overcritical to stress this point, but Curtis⁴ described a case which presented a clinical picture identical with Case 1, and yet the *Micrococcus catarrhalis* was isolated from the joints. Pharyngeal *Neisseria* occasionally cause meningitis, and unless careful bacteriologic study is made, these organisms may be often called meningococci. Sophian³³ cites a case of his own and calls attention to the literature on this point. Thus it seems best to establish the diagnosis of purulent meningococcal arthritis on bacteriologic grounds rather than clinical circumstantial evidence.

It is interesting to review the prognosis of the few cases of proven meningococcal arthritis. The prognosis of the acute synovitis is uniformly excellent, but when the joint space is involved the prognosis should be a little more guarded. In the series of 16 cases reported by Herrick and Parkhurst,¹² there were 2 deaths and a flexion deformity of the knee. These authors also mention 1 case of "necrosis of the head of the radius" following meningococcus arthritis of the wrist. Of Schein's³¹ 23 cases, only 4 were proven by culture; but of these 4, 2 had ankylosis of the joints and the other 2 had limitation of function of the joints. Joe¹⁵ cites 21 cases of arthritis with ankylosis of a shoulder in 1 case. Place²⁴ had 3 joint effusions, but all recovered full joint function. Our Case 1 showed Roentgen ray evidence of bone destruction in the right wrist joint and there was permanent impairment of joint function; Case 2 recovered completely.

From these 66 cases of meningococcal arthritis, not all of which were proven, at least 8 (12%) showed permanent joint changes. If we considered only the cases proven bacteriologically the percentage would be very much increased; for example, of Schein's proven cases, all of them showed permanent joint changes. From these meager data it seems justified to say that the prognosis of meningococcal arthritis is not as favorable as the literature would lead one to believe.

Purulent meningococcal arthritis should be treated conservatively. The effusion frequently resolves spontaneously, but large ones may call for repeated aspirations. Place²⁴ mentions washing the joint out with physiologic saline solution, and if sterile precautions are observed this procedure may be of service. Arthrotomy seems to have no place in the treatment of meningococcal arthritis, not that it would not serve to drain infection, but because it is more radical surgery than is necessary. Although pain is said not to be a prominent feature of these effusions, it may be present as in Case 1, and appropriate splinting with plaster shells may give great comfort to the patient. Similarly, analgesics may be called for and, if pain indicates it, opiates may be resorted to, since the condition is acute rather than chronic. The wide usage of sulfonamide medications in the treatment of meningococcal infections may be expected to lessen the incidence of metastatic manifestations—arthritis among them. As some authors¹⁵ have suggested, if arthritis persists, a second course of sulfonamide medication may be given; this would seem to be necessary only if organisms be cultured from the joint fluid.

Comment. When arthritis is the presenting symptom of a meningococcal infection, it is not always easy to establish the etiology without awaiting cultural demonstration of the organism. In cases of chronic meningococcemia, the septicemia may exist for months prior to the development of meningitis, and the chills, fever, rash and arthralgia may be assigned to other causes than a meningococcal infection. The fever may simulate tertian or quartan malaria,⁶ and the rash and enlarged spleen may lead to the mistaken diagnosis of typhoid fever or subacute bacterial endocarditis. The form of arthritis presented may duplicate that seen in gonococcal infections, and confusion on this score is enhanced by the fact that positive gonococcal complement-fixation tests have been repeatedly reported in proven meningococcal infections.^{7,16,26,31} In our Case 1 the gonococcal complement-fixation test was positive on three separate occasions. The rash may take various forms and imitate Rocky Mountain spotted fever or typhus fever. Haverhill fever was strongly suspected in Case 1 because of the fulminating arthritis and the marked rash on the lower extremities. Dr. L. E. Sutton, who originally described Haverhill fever,²⁵ saw our case in consultation and agreed that the clinical resemblance was so striking that only bacteriologic evidence would establish the diagnosis. The confusion with Haverhill fever has been previously noted.¹⁶

Conclusions. The arthritis commonly referred to in connection with meningococcal infections is in most cases an acute synovitis which occurs concomitantly with the rash. Acute synovitis usually promptly subsides with complete restoration of joint function, but exceptionally the synovitis by extension leads to a purulent arthritis and effusion into the joint space. Purulent meningococcal arthritis is a relatively uncommon disease and not many cases have been proven bacteriologically. It is suggested that the prognosis of this disease is not so uniformly favorable as is usually stated in the literature. Two proven cases of purulent meningococcal arthritis are presented.

We wish to acknowledge our thanks to Dr. William B. Porter, Professor of Medicine, Medical College of Virginia, Richmond, Va., for the privilege of reporting these cases which were seen on the Medical Service of the Medical College of Virginia Hospital.

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SARCOIDOSIS OF BOECK . METABOLIC STUDIES OF 3 CASES

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SARCOIDOSIS is regarded as a generalized systemic disease which may involve almost any organ of the human body. Skin lesions of this condition were first described in 1869 by Hutchinson,⁹ who later suggested the name "Mortimer's malady," because his first patient presenting these manifestations was named Mortimer. In 1889, Besnier² reported a somewhat similar condition involving the face, nose and ears, which was named "lupus pernio." However, it was not until 1899 that Boeck³ published a description of "multiple benign sarcoid" involving skin, mucous membranes and lymph nodes, from which the term sarcoidosis is taken. Following this, Heerfordt⁸ described the uveoparotid syndrome, Kuznitsky and Bittorf¹⁵ reported pulmonary lesions, and Jungling¹² published reports concerning alterations in bone. To Schaumann^{21,22} goes the credit for first suggesting in 1914 the essential identity of these apparently unrelated clinical entities as seen through the eyes of dermatologists, ophthalmologists and other specialists. Schaumann pointed out that sarcoidosis may exist in the absence of cutaneous lesions and that the lymph nodes, tonsils, liver, spleen, bone marrow and lungs are frequently involved.

Recently, pulmonary lesions with and without hilar lymphadenopathy have been reported¹⁴ that have certain characteristics in common. These lesions have been variously named as *granulie froide*, chronic miliary tuberculosis,²⁵ pulmonary tuberculids and *granulie discrete*. As seen on the chest roentgenogram, they are distributed fairly symmetrically and may consist of pseudomiliary or larger foci. Clinically these pulmonary findings are identical with those frequently seen in patients with the lupus pernio of Besnier, Boeck's sarcoid, or Heerfordt's uveoparotid syndrome. This fact alone offers some justification to Schaumann's contention that the identity of the conditions is the same. Additional interest in the problem of sarcoidosis was stimulated in this country by Longcope and Pierson,¹⁶ whose work added further support to Schaumann's observations. In 1938 Pinner¹⁸ reported clinical, histologic and biologic similarity in many cases diagnosed as Boeck's sarcoid, uveoparotid fever, Mikulicz's syndrome, ostitis tuberculosis multiplex cystoides and a number of disseminated pulmonary and lymph node lesions.

The etiology of this condition remains unsettled. Reported cases vary in age from a few months to 60 or more years; however, more cases seem to occur in the 3rd or 4th decade of life. Earlier case reports were mostly of white patients, but a high percentage of recent cases reported were Negro patients. The two sexes seem to be about equally involved. Boeck suggested defective blood formation or auto-intoxication, while Schaumann assumed a tuberculous etiology (probably bovine) and cited several instances in which autopsies ultimately disclosed diffuse, caseating tuberculosis. Pinner regards sarcoidosis as a form of "non-caseating tuberculosis," and states that the sarcoid tubercle must be considered an extreme form of productive reaction in tuberculosis. As further proof, Pinner adds that "in undoubted foci tubercle bacilli are increasingly difficult to demonstrate the more the productive lesions predominate." Biologically it is interesting to note that a large percentage of these patients react only slightly or not at all to tuberculin. Pinner and co-workers¹⁹ utilize this fact in supporting the tuberculous etiology of sarcoidosis because it has been shown that rats respond to the introduction of tubercle bacilli by the formation of lesions that greatly resemble the sarcoid lesions in man, and that rat serum contains tuberculin neutralizing factors (anticutins). English workers¹⁴ have explained the features of sarcoid disease as a result of moribund or dead tubercle bacilli passing into the circulation and producing generalized lesions. Williams and Nickerson²⁶ prepared an antigen from sarcoid tissue which in 4 cases produced skin reactions within 24 hours by intradermal test. They suggested that, as in the case of lymphogranuloma inguinale, sarcoid is probably also a virus disease. Rubin and Pinner²⁰ have recently reviewed the autopsied cases in the literature and concluded that they could add little to the solution of the etiologic question.

Pathologically, the typical lesion is the so-called "hard tubercle," which consists of a microscopic collection of large, pale staining, polygonal, epithelioid cells forming a mass about the size of a miliary

tubercle. Although these cells are not always concentrically arranged, they may be fitted together like tiles in the floor. These clusters of cells are usually isolated, have a minimal peripheral inflammatory reaction, and are without central necrosis, according to some investigators.^{3,17,18} Rubin and Pinner,²⁰ however, report caseation and necrosis in a few cases. Giant cells are common but not always present, and may contain inclusions of various sizes and shapes which stain with hematoxylin. Another characteristic of these lesions is that acid-fast rods are usually not demonstrable and that they are usually sterile, both in culture and in animal inoculations. The tubercles are reported to remain unchanged for long periods of time and to increase in numbers, rather than in size. They heal by a process of fibrosis and hyalinization. These sarcoid lesions may occur in any organ of the body but are prone to appear in lymphoid tissues.

The signs and symptoms of the disease vary with the location and extent of the lesions. Malaise, weakness, drowsiness, anorexia, weight loss, low grade fever, night sweats, dry mouth and generalized aches and pains are found in some patients. Dyspnea and right heart failure have been found in individuals with diffuse pulmonary involvement¹ and a chronic non-productive cough is not uncommon where the lungs or mediastinal lymph nodes are involved. Patients with Heerfordt's syndrome may complain of puffiness of the eyelids, failing vision, facial paralysis and parotid swelling. Involvement of the bones of the hands or feet may prompt complaints of swelling or pain in the fingers or toes. Tillgren²⁴ has reported diabetes insipidus, while Longcope¹⁷ mentions a patient with involvement of testes and epididymis and subsequent loss of secondary sexual characteristics. Cases of generalized sarcoidosis with electrocardiographic and other evidences of cardiac involvement which may vary in different patients are also reported.¹¹ Patients may present themselves with skin lesions or enlarged glands and have no complaints except awareness of their physical findings.

Laboratory studies may reveal a leukopenia with a relative increase in monocytes or eosinophils, while the red blood count usually falls within normal limits. Metabolic studies have revealed elevation of serum protein with reversal of the albumin-globulin ratio. Harrell⁷ has reported blood calcium values at or above the upper limit of normal in 6 of 11 cases, phosphatase levels (presumably alkaline phosphatase determinations) above normal in 7 cases, and blood cholesterol values within normal limits in all patients.

Diagnosis is based on the history of skin lesions, possible lymphadenopathy, Heerfordt's syndrome, tired feeling, irregular fever, failing vision, cough and other symptoms previously mentioned. Slit-lamp examination may reveal an active uveitis, even in the absence of eye complaints. Roentgenographic studies of the chest may reveal hilar and pulmonary involvement and Roentgen rays of the hands and feet may show areas of rarefaction and reticulation distributed throughout the medulla of the phalanges, sometimes with irregular enlargement and distortion of the bones, but without involvement of the periosteum

or of the joints.²³ Tuberculin tests are usually negative in these patients. Blood studies as previously mentioned may aid in the diagnosis. Biopsy of one of the lymph nodes is necessary for absolute diagnosis.

Prognosis in sarcoidosis is disputed and depends on such factors as age, location and extent of lesions, presence of cardiac lesions, and presence of secondary infection. Spontaneous healing of the lesions has occurred in some patients,¹³ while other cases succumb to tuberculosis, cardiac failure, or some other associated condition.

Treatment has been largely symptomatic. Boeck suggested arsenic, while more recently Roentgen ray therapy has been tried. Ophthalmologists have suggested fever therapy in cases of uveoparotid fever.

Case Reports. The following 3 cases are presented, both because of fairly complete metabolic studies having been determined, and because they include 2 additional cases of uveoparotitis.



FIG. 1.—Photograph of Case 1 showing enlarged right lacrimal gland and bilateral parotid enlargement.

CASE 1. E. M. C., a 19 year old colored female, was admitted to Charity Hospital January 29, 1944. Her illness began in September, 1943, when slightly painful swellings at the angle of both jaws were noticed. About the same time she observed that a non-productive cough had developed. In November, 1943, haziness of vision in the right eye first developed. Three days prior to admission puffiness about the eyes developed. The patient had mumps at the age of 6. There was no history of tuberculosis in the family.

Physical examination on admission revealed enlargement of both lacrimal glands (Fig. 1); both parotid glands were enlarged, especially the right, and were not tender. Examination of the right eye showed a large, inflammatory

cauliflower cyst of the iris at 7 o'clock near the margin and a smaller cyst of the iris at 5 o'clock nearer the base (Fig. 2). Slit-lamp study of the right eye revealed numerous, grayish, keratitic precipitates of various sizes, and inflammatory cells were present in the aqueous humor. Many postsynechial and lens precipitates were also seen. The left eye appeared normal. The inguinal nodes were moderately enlarged and the epitrochlear nodes were palpable bilaterally. The remainder of the physical examination was negative.

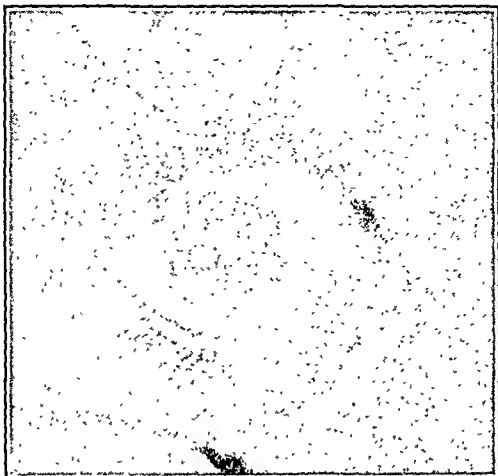


FIG. 2.—View of right eye of Case 1. Notice cysts of the iris.

Laboratory Data. R.B.C, 4,720,000; hemoglobin, 103% (14.9 gm., Hellige); W.B.C, 1800; neutrophils, 47%; eosinophils, 6.5%; basophils, 1.5%; monocytes, 14%; lymphocytes, 31%; platelets, 174,000 (direct); hematocrit (Wintrobe), 44; mean corpuscular volume, 93 microns; mean corpuscular hemoglobin, 31 micromicrograms; and sickling preparation negative. Kline and Kolmer were negative. Blood chemical studies were as follows: serum protein, 8 mg. %; albumin-globulin ratio, 1.0-1.1; blood urea nitrogen, 12.5 mg. %; cholesterol, 156 mg. %; icterus index, 6; serum calcium, 9.9 mg. %; serum phosphorus, 4.5 mg. %; serum alkaline phosphatase, 12.2 (Bodansky units); serum acid phosphatase, 0.8 (normal 0.5-2.5 units); and serum chlorides, 580 mg. %. Sternal bone marrow was normal. Agglutinations for typhoid, para-typhoid A and B, brucellosis, tularemia, and typhus fever were negative. Urinalysis was negative. Sodeman-Engelhardt urinary concentration test showed maximum specific gravity of 1.024 at the end of 2 hours. Phenolsulphone-phthalein test revealed 80% excretion at the end of 1 hour. Bence-Jones protein was not found in the urine. Mantoux tests were negative. Sputum was repeatedly negative for tubercle bacilli. Stools were negative. Vital capacity was 2800 cc. (75% normal). Roentgenogram of the chest (Fig. 3) revealed bilateral hilar enlargement with diffuse infiltration throughout both lungs which appeared to radiate out from the hilum. Roentgenographic examination of the hands, feet, long bones, skull, and pelvis were normal. Electrocardiogram was within normal limits. Biopsy of inguinal nodes on 2 occasions as reported by Dr. Ernest Stark, Department of Pathology, Tulane University of Louisiana School of Medicine, revealed (Fig. 4) "almost complete replacement of the normal lymph node architecture by small and medium sized circumscribed areas composed chiefly of large epithelioid cells arranged in a concentric manner, with a moderate number of lymphocytes near the periphery. Fibers of hyaline connective tissue surround each lesion and delimit it from its neighboring lesion. Giant cells are present in an occasional lesion. Caseation necrosis is minimal and is present only in a few of the circumscribed areas."

The first week in the hospital this patient ran an irregular low grade fever which was never greater than 99.6°. Repeated chest roentgenograms and blood studies were essentially the same as on admission. The patient im-

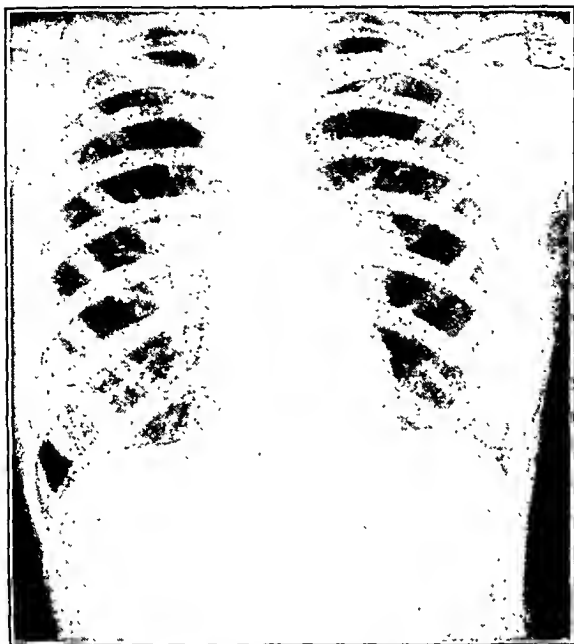


FIG. 3.—Chest roentgenogram of first patient revealing marked bilateral hilar enlargement with diffuse infiltration radiating toward the periphery.

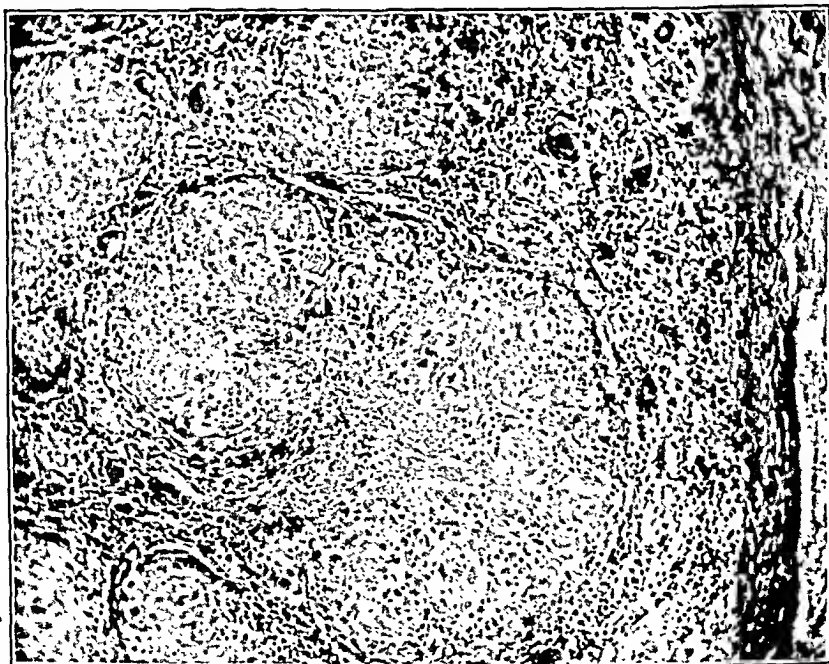


FIG. 4.—Microscopic section ($\times 400$) of inguinal lymph node of Case 1 showing sarcoid lesion.

proved clinically and was discharged to the out-patient department on March 4, 1944.

CASE 2. H. J., a 16 year old colored male, was admitted to the hospital February 3, 1944, with complaints of malaise and a chronic cough since December, 1943. His cough had been non-productive. A history of a 25 pound weight loss in the past year was obtained, and a story of pleuritic pain on the right side 6 months prior to admission was given. There was no history of contact with tuberculosis.

Physical examination revealed a generalized enlargement of the cervical lymph nodes, while there was a suggestive enlargement of the right parotid gland. The axillary nodes were also enlarged but non-tender. The lacrimal glands were not palpable and slit-lamp examination showed both eyes to be apparently normal. The remainder of the physical examination was normal.

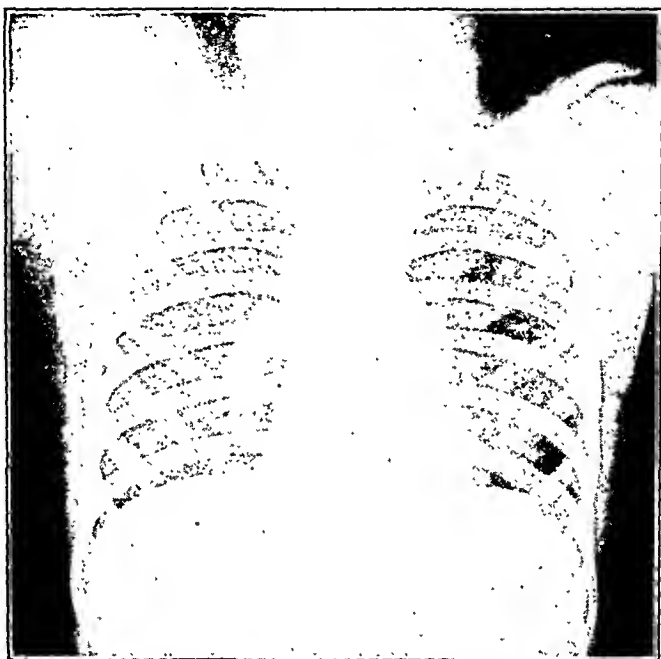


FIG. 5.—Chest roentgenogram of Case 2. Notice hilar enlargement, thickened interlobar pleura on right, and diffuse infiltration.

Laboratory Data. R.B.C., 5,540,000; hemoglobin, 90% (13 gm., Hellige); W.B.C., 5550; neutrophils, 65.5%; eosinophils, 5%; basophils, 0.5%; monocytes, 16%; lymphocytes, 13%; platelet count, 68,400 (direct); hematocrit (Wintrobe), 40; mean corpuscular volume, 72 microns; mean corpuscular hemoglobin, 23 micromicrograms; and sickling preparation, negative. Bone marrow was normal. Kline and Kolmer tests were negative. Blood chemical studies were as follows: blood urea nitrogen, 14.3 mg. %; blood sugar, 96 mg. %; icterus index, 8.6; cholesterol, 196 mg. %; serum protein, 9.64 mg. %; albumin-globulin ratio, 1.0-1.2; serum calcium 11 mg. %; serum phosphorus, 4.5 mg. %; serum alkaline phosphatase, 17.5 (Bodansky units); and serum acid phosphatase, 2.4 (0.5-2.5 units, normal). Agglutinations for typhoid, paratyphoid A and B, brucellosis, tularemia, and typhus fever were negative. Stools were negative. Urinalysis was negative. Phenolsulphonephthalein test revealed 65% excretion at the end of 2 hours. Sodeman-Engelhardt urinary concentration test disclosed maximum specific gravity of 1.028 at the end of 2 hours. Bence-Jones protein was not found in the urine. Mantoux tests were repeatedly negative. Sputum examinations did not reveal tubercle bacilli. Vital capacity was 3100 cc. (70% of normal). Electrocardiograms were

normal. Roentgenographic examination of the chest (Fig. 5) revealed bilateral hilar enlargement, thickening of the interlobar pleura on the right side, and diffuse infiltration radiating out from the hilar regions (more marked on the right). Roentgen ray studies of the bones of the hands, feet, skull, pelvis, and spine were negative. Biopsy of an axillary node revealed a microscopic picture almost identical with that described in the first case.

This patient had no temperature elevation during his period of hospitalization, except for a period of 36 hours following lymph node biopsy. He was comfortable during hospitalization and blood chemistries and roentgenographic findings did not change appreciably. He was discharged to the out-patient department March 17, 1944.



Fig. 6.—Photograph of Case 3. Notice right lacrimal and bilateral parotid enlargement.

CASE 3.* F. J., a 17 year old colored male, was admitted to the hospital March 3, 1944, from the out-patient department because of generalized lymph node enlargement. He became aware of swelling of the neck early in January, 1944, and coughed frequently. This patient also gave a history of fever and night sweats. He had previously had mumps and gave no history of contact with tuberculosis.

Physical examination on admission revealed a temperature of 100° F. Cervical, axillary, epitrochlear, and inguinal lymph nodes were moderately enlarged, discrete, non-tender and were not attached to skin or bone. Lacrimal and parotid glands were not enlarged. Eyes appeared to be normal. The remainder of the physical examination was negative. On March 5, 1944, it was noticed that the patient's parotid glands were enlarging (Fig. 6), were firm, and not tender. The right lacrimal gland was enlarged at this time. On

* F. J. (Case 3) developed a small pleural effusion on the right in May, 1944. Thoracentesis was done, and 2 guinea pigs were injected without producing evidences of tuberculosis or other diseases. The patient deserted the hospital in June, 1944, and was next seen on October 5, 1944, at which time he complained of fever, sweats, and expectoration of bloody sputum. Roentgenogram of the chest at this time revealed an extension of the infiltrative process with several small areas suggestive of cavitation in the right upper lobe. Two of three sputum examinations have been positive for tubercle bacilli.

March 6, 1944, slit-lamp examination of the right eye revealed numerous, scattered keratitic precipitates of various sizes, mostly grayish in color. Numerous inflammatory cells were seen in the aqueous humor while the anterior vitreous showed many scattered, grayish, inflammatory, cellular infiltrations. Findings in the left eye were similar but less marked. On March 30, 1944, skin lesions were first noticed on the lateral aspects of both thighs. These lesions were small, firm, and slightly elevated. They were somewhat paler than the surrounding skin areas.



FIG. 7.—Chest roentgenogram of Case 3. Notice bilateral hilar enlargement with diffuse infiltration of both lungs which is more marked centrally and fades peripherally.

Laboratory Data. R.B.C., 4,600,000; hemoglobin, 92% (13.3 gm., Hellige); W.B.C., 6200; neutrophils, 66%; eosinophils, 6%; basophils, 1%; monocytes, 16.5%; lymphocytes, 10.5%; platelet count, 120,000 (direct); hematocrit (Wintrobe), 40; mean corpuscular volume, 80 microns; mean corpuscular hemoglobin, 28 micromicrograms; and sickling preparation was negative. Bone marrow was normal. Kline and Kolmer were negative. Blood chemical studies were as follows: blood urea nitrogen, 9.5 mg. %; blood sugar, 89 mg. %; icterus index, 8; cholesterol, 240 mg. %; serum chlorides, 590 mg. %; serum protein, 8.9 mg. %; albumin-globulin ratio, 1.0-1.1; serum calcium, 10.4 mg. %; serum phosphorus, 4.5 mg. %; serum alkaline phosphatase, 11.2 (Bodansky units); and serum acid phosphatase, 2.2 (normal, 0.5-2.5 units). Agglutinations for typhoid, paratyphoid A and B, brucellosis, tularemia, and typhus fever were negative. Urinalysis was negative. Sodeman-Engelhardt urinary concentration test disclosed a maximum concentration of 1.028. Phenol-sulphonephthalein test revealed 80% excretion at the end of 2 hours. The urine did not contain Bence-Jones protein. Mantoux test was 2+ positive (1-1000). Sputum examinations were negative for tubercle bacilli and fungi. Sputum cultures were negative. Electrocardiograms revealed a P-R interval

of 0.20 second which was considered long for age and heart rate (88). Roentgenographic examination of the chest (Fig. 7) revealed bilateral hilar enlargement and infiltration in both lungs, the infiltration being more marked centrally and fading out peripherally. Roentgen rays of the bones of the hands, feet, skull, pelvis, and spine were regarded as normal. Biopsy of an axillary lymph node revealed a microscopic picture compatible with sarcoidosis. Biopsy of a skin lesion also disclosed microscopic lesions considered typical of sarcoidosis.

This patient has remained in the hospital for a period of 6 weeks and his temperature has varied from 99.0° to 102.4° F. daily. He has lost 10 pounds during hospitalization. Repeated roentgenographic and blood studies have added little of value. His electrocardiograms continue to show an abnormally long P-R interval of 0.20 second.

Discussion. Some effort was made by us to contribute toward the etiology of sarcoidosis. Guinea pig inoculations with material from the first and second cases were negative. An antigen prepared from a lymph node of the second patient failed to produce positive intradermal reactions. An effort by Dr. Ernest Stark, Department of Pathology, Tulane University of Louisiana School of Medicine, to demonstrate "anticutins," according to the method of Pinner and co-workers,¹⁹ was unsuccessful.

In 1940 only about 100 cases of Heerfordt's syndrome were to be found in the literature,^{4,6} while only 20 were from North America. The author has found 10 cases reported since 1940. Uveoparotitis was present in 2 of the 3 cases reported here. Each of these cases presented pulmonary and lymph node involvement, while skin lesions were found in only 1.

A recent report¹¹ indicates that only 8 proven cases of sarcoidosis of the heart have been reported thus far. Undoubtedly, many other cases have occurred. Although other causes, such as an unrecognized previous rheumatic process, could not be definitely excluded, it is entirely possible that the prolonged P-R interval (0.2 second) of the third patient may have been an indication of sarcoid lesions in the heart.

Leukopenia and eosinophilia were demonstrable in each of the cases reported. Red blood counts and hemoglobin values were essentially normal.

Although Harrell⁷ reported in 1940 that serum phosphatase levels are increased in sarcoidosis, no technique was generally available at that time^{5,10} to determine serum acid phosphatase values. Serum alkaline phosphatase levels were elevated in each of these 3 cases, while serum acid phosphatase values were not affected.

Blood calcium, phosphorus, cholesterol, glucose and urea studies revealed values within the generally accepted limits of normal.

Summary. 1. A brief review of the historical, etiologic, pathologic and clinical aspects of sarcoidosis is given.

2. Three cases, including 2 with Heerfordt's uveoparotid syndrome, are presented.

3. The possibility of sarcoid lesions of the heart in 1 case is discussed.

4. Serum acid phosphatase values of these 3 cases were found to be within normal limits, while serum alkaline phosphatase values were elevated.

5. Other metabolic studies merely confirm findings previously reported by other investigators.

6. No additional information concerning the etiology was revealed by these studies.

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ELECTROPHORETIC ANALYSIS OF PLASMA PROTEINS IN HYPERTHYROIDISM AND HYPOTHYROIDISM

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STUDIES of the plasma proteins in thyroid disease have been rather fragmentary. In 1932 Shirer¹⁴ reviewed the literature and reported 75 cases in which the total serum protein, albumin, euglobulin, pseudoglobulin I, and pseudoglobulin II were determined. In hyperthyroidism he found a definite decrease in serum albumin and an increase in total globulin. There was a decrease in pseudoglobulin II, while pseudoglobulin I and euglobulin were increased. The average albumin-globulin ratio ranged from 0.61 to 0.70 in different groups. In hypothyroidism reversal persisted, the ratio being 0.89 in 12 cases.

Our studies were undertaken because fractionation of serum proteins

by the salting-out technique is open to considerable criticism and because electrophoretic analyses of plasma proteins in thyroid disease have not been reported.

Methods. Protein Studies. A fasting blood sample was taken and oxalated, using 1.5 mg. potassium oxalate per milliliter of blood. The blood was immediately centrifuged at high speed and the plasma removed. Total plasma nitrogen was determined on an aliquot of plasma by the Pregl¹³ modification of the micro-Kjeldahl method. If the blood urea nitrogen was within normal limits, a non-protein nitrogen correction of 25 mg. per 100 ml. was used. If the blood urea nitrogen was elevated, the non-protein nitrogen was determined and the proper correction made. The value 6.25 was the protein factor used. Five ml. of plasma was diluted 1 to 4 with phosphate buffer of pH 7.8 and ionic strength 1.6. The diluted plasma was dialyzed 72 hours at approximately 3° C. in a cellophane sac against the phosphate buffer solution. At the end of dialysis the diluted plasma was centrifuged at high speed. Studies were done in the Tiselius electrophoresis apparatus by Longsworth's⁸ modification of the Tiselius method. Pattern areas were determined by the procedure of Tiselius and Kabat.¹⁵

TABLE 1.—PLASMA PROTEIN FRACTIONS OF NORMAL SUBJECTS

Subj. No.	Sex	Total protein (gm.*)	Albumin		α -Globulin		β -Globulin		γ -Globulin		Fibrinogen		A/G†
			Gm.*	%†	Gm.*	%†	Gm.*	%†	Gm.*	%†	Gm.*	%†	
1	F	6.85	4.48	65.6	0.50	7.3	0.80	11.7	0.70	11.6	0.26	3.8	2.12
2	F	6.93	4.42	63.0	0.49	7.1	0.97	14.0	0.85	12.2	0.20	2.8	1.90
3	F	7.46	4.53	60.9	0.65	8.7	1.02	13.5	0.91	10.1	0.35	6.8	1.75
4	F	6.33	4.02	63.4	0.52	8.1	0.78	12.3	0.78	12.2	0.22	3.2	1.93
5	F	6.52	3.97	60.8	0.52	8.0	0.88	13.4	0.72	11.1	0.43	6.7	1.87
6	M	6.31	3.84	60.9	0.41	6.5	1.00	15.9	0.76	12.0	0.30	4.7	1.77
7	F	7.82	5.11	65.3	0.66	7.2	1.07	13.7	0.76	9.7	0.32	4.1	2.14
8	F	6.57	3.97	60.3	0.55	8.4	0.73	11.3	0.90	13.7	0.42	6.4	1.84
9	M	6.09	3.74	61.4	0.51	8.4	0.68	11.2	0.90	14.8	0.26	4.2	1.79
10	M	5.94	3.84	64.6	0.40	6.6	0.65	11.0	0.71	12.0	0.34	5.8	2.18
11	M	6.39	4.19	65.6	0.42	6.5	0.86	13.5	0.55	8.6	0.37	5.8	2.28
12	F	6.66	4.12	61.9	0.47	7.1	0.84	12.5	0.75	11.3	0.48	7.2	2.00
13	F	6.87	4.21	61.3	0.42	6.1	0.99	14.4	0.83	12.1	0.42	6.1	1.88
14	M	6.58	4.08	60.5	0.40	6.0	0.90	12.9	0.90	12.9	0.50	7.7	2.04
15	F	5.98	4.02	67.2	0.40	6.6	0.67	11.3	0.60	10.0	0.16	4.9	2.22
16	M	6.40	4.25	66.3	0.50	7.8	0.78	12.3	0.63	9.8	0.24	3.8	2.22
17	M	6.48	3.90	60.1	0.43	6.6	0.92	14.3	0.87	13.5	0.36	5.5	1.75
18	M	6.12	3.76	61.5	0.42	6.9	0.84	13.7	0.77	12.5	0.33	5.4	1.85
19	F	5.99	3.72	62.1	0.39	6.5	0.77	12.7	0.74	12.2	0.39	6.5	1.98
20	F	6.25	3.95	63.3	0.41	6.5	0.96	15.4	0.71	11.3	0.22	3.5	1.90
21	M	6.12	3.82	62.3	0.46	7.5	0.81	13.3	0.70	11.5	0.33	5.4	1.94
Average	..	6.51	4.09	62.7	0.47	7.2	0.81	13.1	0.77	11.7	0.33	5.4	1.97
Range	..	5.94-7.82	3.72-5.11	60.1-67.2	0.39-0.66	6.0-8.7	0.65-1.07	11.0-15.9	0.60-0.91	8.6-14.8	0.16-0.48	2.8-7.2	1.75-2.28

* Grams per 100 ml. plasma.

† Percentage of total protein.

‡ Albumin-globulin ratio calculated on serum basis.

Subjects. Control values were determined on blood from 21 laboratory workers and physicians. These subjects were from 20 to 45 years old and had no abnormal physical findings.

Twenty patients with hyperthyroid or hypothyroid symptoms were studied. In all hyperthyroid cases an elevated basal metabolic rate with concurrent physical findings typical of the disease was present. Criteria for decreased thyroid function were an abnormally low basal metabolic rate, myxedema, and elevated blood cholesterol in addition to characteristic physical abnormalities.

Twelve patients were studied who had progressive exophthalmos following thyroidectomy or Roentgen ray irradiation of the thyroid. Their basal metabolic rates were within normal limits, and exophthalmos was the only remaining visible symptom of the thyroid syndrome.

Results. Normal values agree closely with those reported by Longsworth and co-workers,⁹ Luetscher,¹⁰ and Moore and Lynn as cited by Abramson and co-workers¹ (see Table 1).

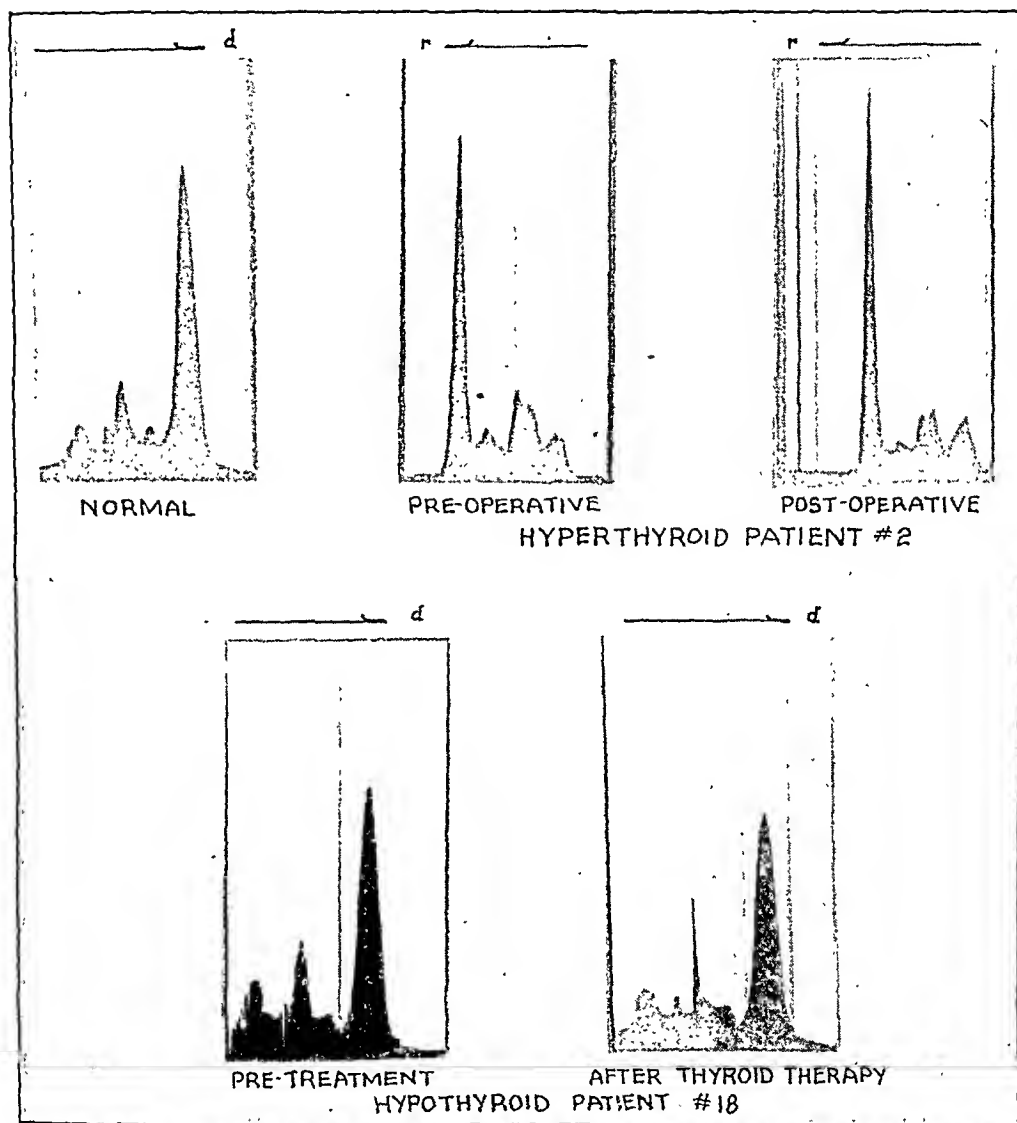


FIG. 1.—Electrophoretic patterns of the descending boundaries of normal human plasma, of the ascending boundaries of plasma from a hyperthyroid patient before operation and 4 months after operation, and of the descending boundaries of plasma from a hypothyroid patient before and after thyroid therapy.

Table 2 gives results for patients with hyperthyroid or hypothyroid symptoms. Series for the same patient are listed as *a*, *b*, and *c* under the patient's number. Successive tests on hyperthyroid Patient 2 and hypothyroid Patient 18 are shown in Figure 1. Figure 2 presents data on Patient 1, a typical hyperthyroid, before and after treatment. Figure 3 represents a series of studies on hypothyroid Patient 17, and Figure 4 a series on Patient 20, a cretin. Values for Patient 25, who had progressive exophthalmos, are seen in Figure 5.

HYPER THYROID

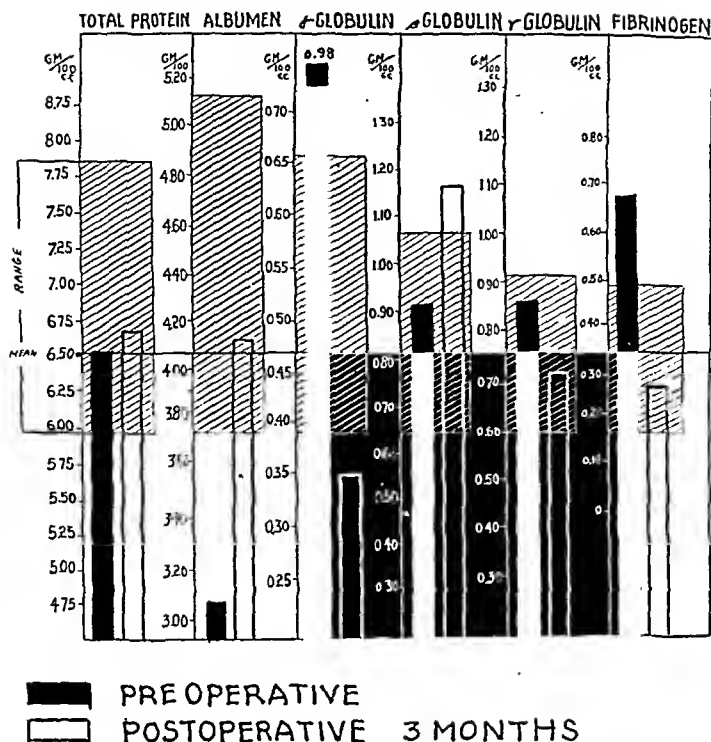


FIG. 2.—Data on Patient 1, a typical hyperthyroid, before and after treatment.

HYPOTHYROID

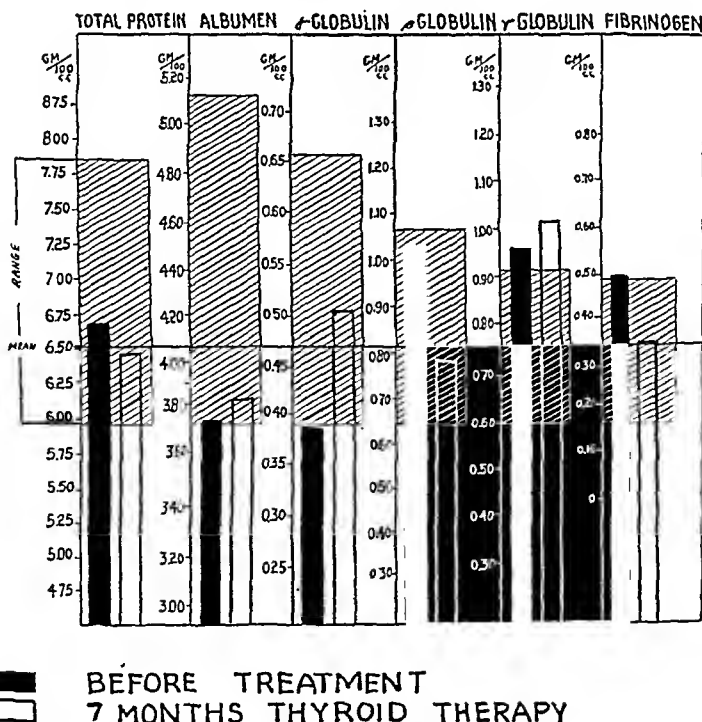


FIG. 3.—Results of a series of studies on hypothyroid Patient 17.
(730)

HYPOTHYROID - CRETIN

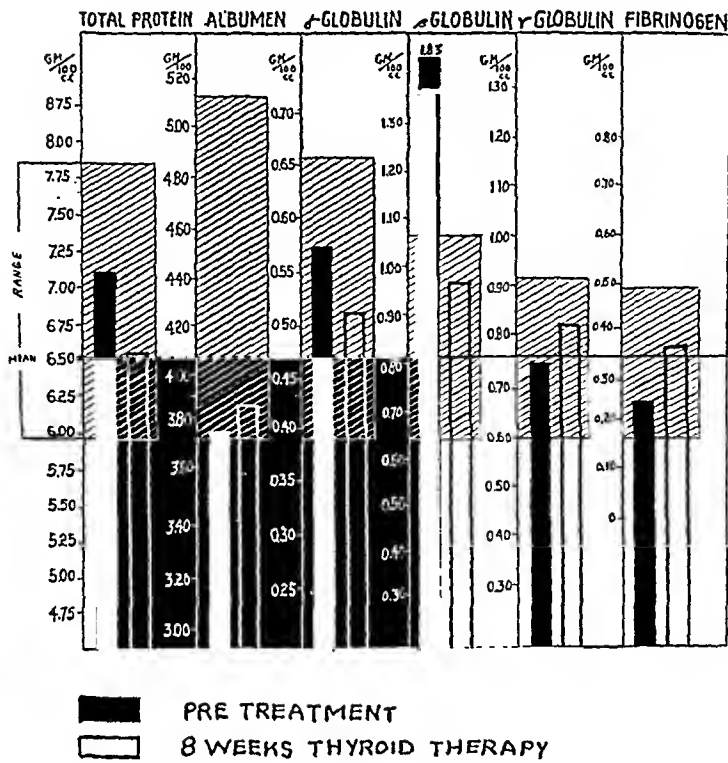


FIG. 4.—Results of a series of studies on Patient 20, a cretin.

PROGRESSIVE EXOPHTHALMOS

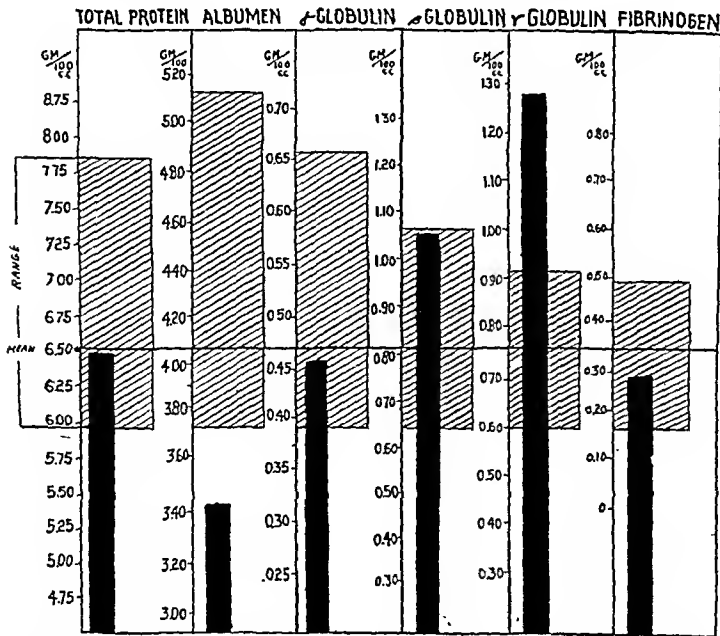


FIG. 5.—Values for Patient 25, who had progressive exophthalmos.

TABLE 2.—PLASMA PROTEIN FRACTIONS OF PATIENTS WITH THYROID DISEASE

Case No.	Type of case	Total protein (gm.%)	Albumin		α -Globulin		β -Globulin		γ -Globulin		Fibrinogen		Body weight change (lb.)
			Gm.*	%†	Gm.*	%†	Gm.*	%†	Gm.*	%†	Gm.*	%†	
1	Hypothyroid												
	a. Preoperative	6.51	3.07	47.3	0.98	14.9	0.91	13.9	0.87	13.4	0.68	10.5	1.11
	b. 3 mos. postoperative	6.05	4.13	62.0	0.35	5.2	1.17	17.7	0.72	10.9	0.28	4.2	1.84
2	Hypothyroid												
	a. Preoperative	6.37	3.58	56.2	1.03	16.1	0.63	9.9	0.78	12.1	0.35	5.5	1.46
	b. 4 mos. postoperative	6.02	3.58	59.4	0.47	7.8	0.65	10.8	0.77	12.8	0.55	9.2	1.90
3	Hypothyroid												
	Preoperative	6.75	3.42	51.0	1.00	14.8	1.05	15.4	0.69	10.1	0.59	8.7	1.25
													+16 (increased appetite)
4	Hypothyroid												
	Preoperative	6.31	3.48	55.0	0.71	11.2	0.78	12.5	0.75	11.9	0.59	9.4	1.55
5	Hypothyroid												
	2 days postoperative	5.05	2.45	48.5	0.53	10.4	0.92	18.3	0.72	14.2	0.43	8.6	1.13
6	Hypothyroid												
	2 days postoperative	6.00	3.45	57.4	0.48	8.1	0.72	12.1	0.64	10.7	0.70	11.7	1.86
7	Hypothyroid												
	Preoperative	6.40	3.62	55.1	0.92	14.3	0.89	13.9	0.66	10.3	0.41	6.4	1.52
8	Hypothyroid												
	Preoperative	6.96	3.56	51.1	0.84	12.1	1.27	18.3	0.92	13.2	0.37	5.3	1.10
9	Hypothyroid												
	Preoperative	6.56	3.70	56.4	0.70	10.6	1.06	16.1	0.60	9.2	0.50	7.7	1.56
10	Hypothyroid												
	Preoperative	5.50	3.03	55.1	0.47	8.5	0.85	15.4	0.77	14.0	0.38	7.0	1.45
11	Hypothyroid												
	Preoperative	6.68	3.77	56.4	0.67	10.0	1.39	20.9	0.51	7.6	0.34	5.1	1.47
12	Hypothyroid												
	Preoperative	6.64	3.64	54.8	0.76	11.4	1.00	15.0	0.81	12.3	0.43	6.5	1.41
13	Hypothyroid												
	a. Preoperative	6.56	3.55	54.1	0.73	11.2	0.87	13.3	0.93	14.1	0.48	9.4	1.38
	b. 9 mos. postoperative	7.02	4.02	58.8	0.63	8.9	0.99	14.1	0.99	14.1	0.29	4.1	1.48
14	Hypothyroid§												
	Preoperative	4.85	2.76	57.0	0.51	10.4	0.64	13.2	0.61	12.5	0.33	6.9	1.57
15	Hypothyroid												
	a. Pretreatment	6.59	3.46	52.6	0.34	5.1	1.07	16.2	1.33	20.2	0.39	5.9	1.26
	b. Fed thyroid 2 wks.	6.67	3.50	52.5	0.34	5.1	1.28	19.2	1.15	17.0	0.40	6.1	1.26
	c. Fed thyroid 5 wks.	6.77	3.76	55.5	0.56	8.3	0.94	13.9	1.01	14.9	0.50	7.4	1.50

Case No.	Previous treatment	Albumin		α -Globulin		β -Globulin		γ -Globulin		Fibrinogen		Body weight change (lb.)
		Gm.*	%†	Gm.*	%†	Gm.*	%†	Gm.*	%†	Gm.*	%†	
16	Hypothyroid											
	a. Pretreatment.	6.68	3.69	55.2	0.33	4.9	1.14	17.2	1.10	16.5	0.42	1.43
	b. Fed thyroid 3 wks.	6.42	3.35	52.2	0.44	6.8	1.00	15.5	1.09	17.0	0.54	1.33
	c. Fed thyroid 5 wks.	6.29	3.58	56.8	0.43	6.9	0.91	14.4	0.98	15.5	0.39	1.54
17	Hypothyroid											
	a. Pretreatment	6.64	3.75	57.2	0.37	5.6	1.02	15.3	0.96	14.5	0.49	1.56
	b. Fed thyroid 6 wks.	6.27	3.80	60.5	0.50	8.1	0.56	8.8	1.02	16.3	0.39	1.83
	c. Fed thyroid 7 mos.	6.48	3.84	59.2	0.51	7.9	0.78	12.1	1.01	15.6	0.34	1.67
18	Hypothyroid											
	a. Pretreatment	6.87	3.94	57.4	0.30	4.3	1.65	24.0	0.67	9.8	0.31	1.50
	b. Fed thyroid 8 wks.	6.82	3.81	55.9	0.53	7.7	1.04	15.3	0.98	14.3	0.46	1.50
19	Hypothyroid											
	a. Pretreatment	6.95	3.90	56.1	0.44	6.4	1.20	17.2	1.10	15.8	0.31	1.42
	b. Fed thyroid 7 wks.	6.46	3.71	57.4	0.50	7.8	0.84	13.0	1.11	17.2	0.30	1.52
20	Hypothyroid cretin											
	a. Pretreatment	7.12	3.74	52.5	0.57	8.0	1.83	25.8	0.73	10.2	0.25	1.19
	b. Fed thyroid 8 wks.	6.52	3.87	59.3	0.51	7.9	0.99	15.1	0.82	12.6	0.33	1.67

* Grams per 100 ml. plasma.

† Percentage of total protein.

† Albumin-globulin ratio calculated on serum basis.
§ Proved liver damage.

TABLE 3.—PLASMA PROTEINS OF PATIENTS WITH PROGRESSIVE EXOPHTHALMOS BUT NO OTHER EVIDENCE OF EXOPHTHALMIC GOITER

Case No.	Previous treatment	Albumin		α -Globulin		β -Globulin		γ -Globulin		Fibrinogen		Body weight change (lb.)
		Gm.*	%†	Gm.*	%†	Gm.*	%†	Gm.*	%†	Gm.*	%†	
21	Röntgen ray to pituitary and thyroid	5.90	3.04	51.6	0.43	7.2	1.04	17.6	1.12	19.0	0.27	0
22	Röntgen ray to thyroid	6.82	3.65	53.2	0.36	5.3	0.88	12.8	1.27	18.5	0.70	0
23	Röntgen ray to thyroid	6.21	4.02	64.6	0.55	8.8	0.76	12.5	0.51	8.2	0.37	0
24	Röntgen ray to thyroid	6.10	3.60	59.3	0.52	8.5	0.85	14.0	0.77	12.6	0.36	0
25	Thyroidectomy	6.49	3.42	52.6	0.46	7.0	1.05	16.3	1.27	19.5	0.29	0
26	Thyroidectomy	6.12	3.52	57.5	0.41	6.7	1.03	16.8	0.76	12.5	0.40	0
27	Thyroidectomy	6.34	3.44	54.3	0.39	6.0	1.13	17.9	0.89	14.0	0.49	0
28	Thyroidectomy	6.56	3.43	52.3	0.65	9.9	1.37	20.9	0.73	11.1	0.38	0
29	Thyroidectomy	6.22	3.24	52.2	0.76	12.2	0.75	12.0	0.97	15.6	0.50	0
30	Thyroidectomy	6.37	3.37	52.8	0.59	9.3	1.03	16.2	0.92	14.4	0.46	0
31	Thyroidectomy	6.11	3.41	55.7	0.70	11.7	0.85	14.0	0.64	10.4	0.50	+15 in 4 mos. §
32	Thyroidectomy	6.15	3.97	64.6	0.41	6.7	0.88	14.3	0.70	11.3	0.19	0

* Grams per 100 ml. plasma.

† Percentage of total protein.

† Albumin-globulin ratio calculated on serum basis.

§ Basal metabolic rate - 10.

In the hyperthyroid cases, the most notable and consistent deviation from the normal was a low albumin, both in grams per 100 ml. and in percentage of total protein. An increase in α -globulin was noted in many instances. In some cases the fibrinogen level was also high. In the 2 cases of greatest elevation of fibrinogen the blood was taken 2 days after operation, which may partially explain this change. The other cases were studied preoperatively.

In the cases studied several months after operation, when all symptoms of hyperthyroidism had subsided, the plasma protein picture was normal or much improved.

In contrast with patients who had no postoperative symptoms and showed a normal or nearly normal plasma protein picture was the group with progressive exophthalmos after thyroidectomy or Roentgen ray irradiation of the thyroid. Of the 12 patients studied, 10 had a strikingly abnormal plasma protein picture (Table 3).

All adult hypothyroid patients had a decrease in percentage of plasma albumin. The β -globulin was greatly elevated and the α -globulin decreased or at a low normal level, both in percentage of total protein and in grams per 100 ml. After treatment the β -globulin always fell and the α -globulin rose. In some cases the percentage of albumin increased, although the actual value in grams per 100 ml. showed no consistent change.

In the cretin case the β -globulin was much elevated, as in the adult hypothyroid cases, but the α -globulin was above normal. However, it may not be valid to compare values obtained on a child with those of normal adult controls.

The decreased plasma albumin noted in the hyperthyroid cases agreed with reported values obtained by chemical fractionation. The values observed in our cases, however, were not as low as those reported when chemical precipitation was used. The average albumin percentage in the hyperthyroid cases was 54, whereas the average normal value was 62.7. The albumin-globulin ratio was also less radically altered. The normal albumin-globulin ratio was 1.75 to 2.28; for hyperthyroids the ratio was 1.10 to 1.86.

Comment. The fact that many hyperthyroid patients have impaired liver function and histologically demonstrable liver damage suggests that liver changes may explain the decreased albumin (Beaver and Pemberton,³ Maddock and others,¹² McIver¹¹). Low serum albumin was a very characteristic change observed by Gray and Barron⁶ in the electrophoretic analysis of serum proteins in diseases of the liver.

Experiments on hyperthyroid dogs by Drill and co-workers⁴ disclosed greatly decreased liver function (as indicated by bromsulfalein excretion), which was evident in animals given the standard diet on an average of 45 days after beginning thyroid feeding. Administration of 10 gm. of yeast concentrate daily (equivalent to 200 U.S.P. units of vitamin B₁, 230 μ g. of riboflavin, 200 μ g. of vitamin B₆, and 1500 to 2000 μ g. of copantothenate per gram) delayed the derangement of liver function until 90 days after initiation of thyroid feeding. These experiments suggested the interesting possibility that the patients with the greatest alteration in plasma proteins were receiving the least adequate

vitamin B-complex diet. Such a thing is difficult to prove when patients have fully developed hyperthyroidism of some duration at the time the first studies are made.

Reversible liver changes could also account for the return of plasma protein levels to normal after abatement of hyperthyroid symptoms.

The low plasma albumin observed in the hypothyroid cases agreed with reported results for thyroidectomized dogs (Goldberg⁵) and rats (Levin and Leatham⁷). In the animal experiments globulins were not fractionated. Our studies showed an increase in β -globulin and γ -globulin fractions. The plasma cholesterol was very high when the β -globulin was most elevated. Experiments of Longworth and associates⁹ on plasma from a patient with obstructive jaundice yielded a very high β -globulin value. The plasma contained a large amount of cholesterol. Extraction with ether reduced the β -globulin peak. According to Abramson and co-workers,² "this suggests a combination between lipids and β -globulin."

Summary. The plasma proteins of 20 hyperthyroid or hypothyroid patients were studied by the Tiselius electrophoresis method. Control values were established on 21 normal subjects.

In the 14 hyperthyroid cases the plasma albumin was below normal levels both in grams per 100 ml. and in percentage of total plasma protein. In the majority of cases the α -globulin was markedly increased. No consistent change was observed in the other globulin fractions. After thyroidectomy, when all symptoms of hyperthyroidism had subsided, the plasma protein picture was normal or had values only slightly beyond the normal range.

In the 6 hypothyroid cases there was a low plasma albumin, a low α -globulin, and an increased β -globulin. After some months of thyroid therapy the plasma protein picture approximated the normal.

In patients with progressive exophthalmos and no other residual symptoms of Graves' disease, there was a low plasma albumin but no consistent change in the globulin fractions.

Dr. Edmund E. Beard kindly furnished blood samples and clinical data on Patient 15.

We wish to acknowledge the services of Mr. V. B. Seitz of the Cleveland Clinic, who helped in planning and construction of the Tiselius apparatus.

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ASPIRATION BIOPSY OF THE THYROID IN THE EVALUATION OF THYROID DYSFUNCTION*

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THERE are numerous clinical and laboratory tests for the diagnosis and evaluation of thyroid dysfunction. Nevertheless there is a group of cases where the laboratory and clinical findings are at variance and a diagnosis cannot be made definitely. The standard procedure for laboratory diagnosis, the basal metabolism test, has certain limitations in its interpretation.⁴ Blood cholesterol levels and the galactose tolerance test are two other valuable laboratory procedures, but they, like the basal metabolism are affected by extrathyroid pathology. Other laboratory tests like the urinary creatinin, the creatinin hydrate tolerance test,¹⁰ the complement-fixation serum test⁶ and the electrical impedance angle test for thyrotoxicosis³ have been discarded for the most part as impractical or unreliable. The blood iodine level is a valuable indicator, but like other laboratory tests is but an indirect measure of thyroid activity. Clinical tests such as the quinine tolerance test,² the thyroid tolerance test,⁸ the adrenalin hypersensitiveness test⁵ and the iodine tolerance test⁹ are likewise limited in their scope and interpretation because the symptoms and signs of thyroid diseases can be closely mimicked by several other organic and functional disorders.

The direct method of tissue examination always stands as the final diagnostic criterion. Biopsy has been used to establish the diagnosis in a variety of diseases in many organs. Where the tissue is approached easily, enough can be excised for ordinary histologic section. Where it is more inaccessible, aspirations have been resorted to, using a needle and syringe. The chief difficulty encountered with aspiration biopsies is that only a very small amount of tissue is obtainable, making the ordinary histologic diagnosis often unsatisfactory.

Abel¹ has utilized a method of histologic diagnosis of thyroid disease based on a micrometric examination of the thyroid acinar cells. Because the method utilizes the dimensions of the cells themselves, and not the general architecture of the gland, it can be used with very small amounts of tissue and thus suggests that aspiration biopsies can be used for the *direct* diagnosis of thyroid disease.

Procedure. In order to make the procedure as simple and as atraumatic as possible, a technique has been followed using either a No. 18 or a No. 16 gauge 2 inch intravenous needle and an ordinary 20 cc. syringe. The needle should be sharp and the syringe fairly new so that the barrel and piston do

* Thesis submitted by the Senior author to the Faculty of the Graduate School of Medicine of the University of Pennsylvania, in partial fulfillment of the requirements for the degree of Master of Medical Science (M.Sc.[Med.]) for graduate work in Surgery.

not fit loosely. A record type or a special aspiration syringe (B. D. & Co.) may be used, but are not necessary. Tissues obtained are placed in 5% formalin and are treated as regular paraffin sections to insure uniformity of results. The tissues cannot be smeared like tumor aspirations as described by Martin and Ellis.⁷ However, to obtain a quick diagnosis, rapid sections can be done as outlined by them.

The patient may be given a sedative 20 minutes before the aspiration. He should be lying flat with the neck slightly hyperextended. The gland is palpated and a small area in the midline of the neck close to the gland is prepared aseptically and a wheal is raised in the skin with 1% procaine. Some of the solution is injected continuously along the line of the intended puncture down to the gland. A small nick is made through the skin with a bistoury pointed scalpel (No. 11 B. P. blade) with the instrument held at right angles to the skin surface. This puncture of the skin facilitates insertion of the needle and prevents the needle becoming plugged with surface epithelium. The needle with the syringe attached is introduced tilted about 30 degrees to the sagittal plane. It is advanced slowly through the superficial tissues until the point is felt to enter one or the other of the lateral lobes, whichever seems more accessible. This technique will avoid the trachea, and other important

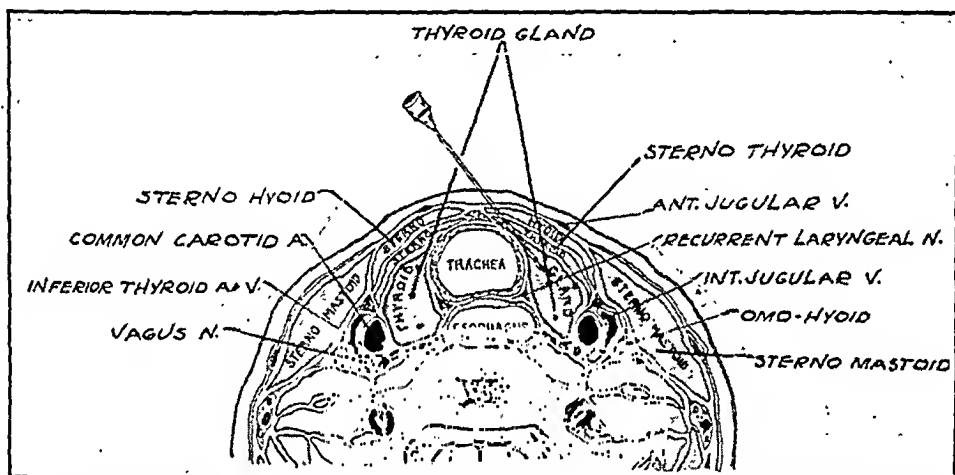


FIG. 1.—Transverse section of neck at level of sixth cervical vertebra illustrating an aspiration needle in place.

structures, as shown in Figure 1. Guided by palpation with the disengaged hand, it is striking how readily a difference in consistency of the tissues can be felt, as the point of the needle enters the gland. When the point of the needle is felt to enter the gland, the piston of the syringe is partly withdrawn so as to produce a vacuum, and the needle is then advanced 1 to 3 cm. farther, depending on the size of the gland. Maintaining the vacuum, the needle is then withdrawn to the same distance, advanced again, and withdrawn, thus maintaining the vacuum constantly and keeping the point of the needle within the gland. As the needle is advanced into the gland, a slightly rotatory motion may be given to the needle. Tissue from the gland enters the needle and is held within it both by a punch action of the advancing needle and by suction of the vacuum. Care must be taken that the vacuum is maintained while the needle is manipulated within the gland. Aspiration by suction alone, with the needle at rest, is usually not sufficient to draw tissue into the needle, and is the most common cause of failure to obtain tissue. In 23 cases we failed to obtain sufficient material for examination in 3.

Before the needle is completely withdrawn from the tissues, the piston must be slowly released, the syringe detached, and the needle withdrawn separately, otherwise any remaining vacuum may cause the aspirated material to be

suddenly drawn into and splashed over the interior of the syringe making its collection more difficult. Blood and tissue usually appear in the syringe while the needle is being advanced and withdrawn. This occurs especially in the diffuse toxic type, or so-called "blotting-paper" gland. In addition, there will most always be tissue in the needle.

After complete withdrawal of the apparatus, the syringe is partially filled with air, again attached, and the contents of the needle expelled into the specimen bottle. If tissue is obtained, the needle and syringe should then be washed with a small amount of the formalin to insure getting all of the material, as some of it may stick to the side of the needle and syringe. If no visible tissue is obtained, the procedure may be repeated, using the same or the contralateral lobe, and going through the same skin puncture.

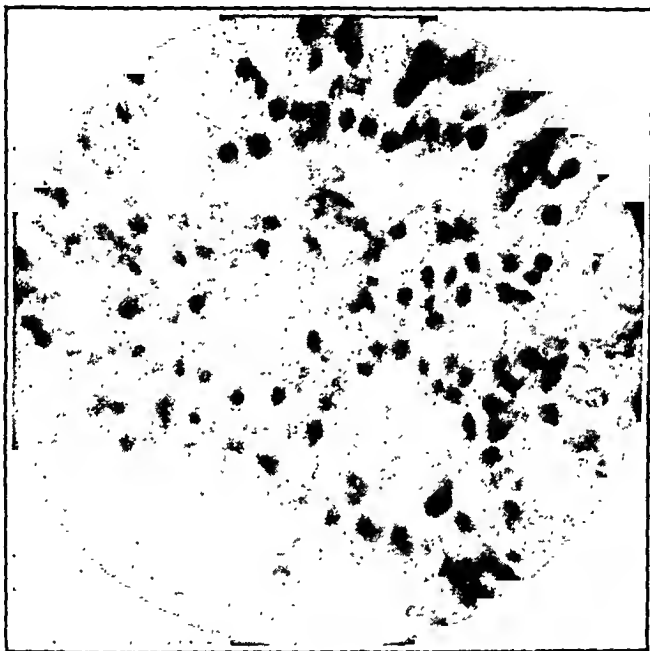


FIG. 2.—Aspiration biopsy of the thyroid gland. (Oil immersion.)

Contrary to what might be expected, if a few minutes are spent explaining to the patient that it is a simple routine examination, it is accepted even by the toxic patient as casually as the basal metabolism test. Most patients on sight of the needle and syringe take it as "just another blood test." It can be done in a few minutes with little discomfort. Occasionally when the needle penetrates quite deeply there may be a slight pain felt in the back of the neck which disappears when the needle is withdrawn.

Thus far the procedure has been absolutely safe in our hands. The first 7 tests were done on the operating table shortly before thyroidectomy to establish the safety of the procedure. In only 1 case (the second) was there any evidence of where the point of the needle had penetrated the gland. In this case we did not conform to our now established technique, and the needle was inserted lateral to the gland and resulted in a small hematoma. We have had no untoward results from the procedure, nor any unpleasantness of any kind. Up to the present the test has been done only upon hospital cases, but there does not seem to be any reason why it cannot be done in any clinic out-patient department or doctor's office.

On microscopic examination the aspiration specimens are found to contain only small particles of the gland itself in amongst much blood. On closer

examination under the oil-immersion lens, these particles are seen to consist entirely of acinar cells, arranged in acini and portions of acini from which the colloid material is entirely gone (Fig. 2). The force of the aspiration is apparently chiefly exercised on the cells, and the colloid is squeezed out and left behind. In those cases where only single cells are left, the acinar cells appear to be intact and undistorted in their acini and remnants of acini. The cell boundaries are as easily distinguishable as in ordinary sections of thyroid. In fact, in some instances the cell borders are more difficult to delineate in whole gland sections, because of the gradual merging of globules of secretory material in the cell with colloid in the acini.

The measurement of the thyroid acinar cells as described by Abel¹ in regular thyroid sections of postmortem specimens was performed with a micrometer scale fitted into the eyepiece of the microscope and using an oil-immersion objective. The diameter of a cell was measured in all cases at a point crossing the nucleus, and on a line along the radius of an acinus. The cells were measured in blocks of 100 from 100 separate acini chosen at random according to where the scale happened to fall as the slide was systematically moved across the stage. The only provisos were that the acini be open and the cell boundaries be distinguishable.

This same technique was used in these experiments in measuring cells in control slides from operative specimens of thyroids from which aspirations had been previously obtained. In the measurement of cells from aspiration specimens, the technique had to be modified slightly because of the fact that in many instances only portions of acini were obtained in the specimens. The diameter of the cell was measured as before, across the nucleus along the apparent line of the diameter of the acinus. The cells were measured in blocks of 100 per aspiration chosen from 100 separate acini or portions of acini, chosen at random as the slide was systematically moved across the stage. The conditions for measurement were that the cell boundaries be distinct, and sufficient of the acinus be left that its apparent contour and radius be readily seen.

With this procedure 100 cells from each of 20 aspiration specimens were measured. Later, sections from surgical specimens were obtained from each of 17 glands (aspiration was done on 3 normal patients with other surgical disorders) and 100 cells from each were measured and the results were compared with those from the aspirations.

Findings. Abel¹ used the criterion that an average cell height of over 5.8 units indicated toxicity in nodular goiters; a height of over 5 units indicated toxicity in diffuse goiters, and a height of less than 5 units indicated a normal gland. Each of his units equalled 1.4 microns giving us the following standards to go by:

1. An average cell height of over 8.1 microns indicates toxicity in nodular goiters.
2. An average cell height of over 7 microns indicates toxicity in diffuse goiters.
3. An average cell height under 7 microns indicates a normal gland.

Using these standards we found that the measurements from all the aspirations were of the magnitude expected (Table 1).

The measurements obtained from the aspiration specimens compared very closely to the measurements obtained from the surgical specimens. The greatest discrepancy was only of a magnitude of 0.7 micron in Cases 1, 6 and 10.

We were able to make the diagnosis of toxicity in 16 cases of the 17 cases examined. In 5 cases of nodular thyroids we were able to establish toxicity and in 11 cases of diffuse hyperthyroidism the diag-

TABLE 1.—CASES OF HYPERTHYROIDISM

Patient	Age	Sex	Physical signs and symptoms	Size of gland palpable to palpation	Av. pulse pressure range	Av. blood pressure	Av. pulse pressure	Basal metabolic rate	Blood cholesterol (mg. per 100 ml.)	Peak galactose tolerance level (mg. per 100 ml.)*	Iodine therapy	Wt. change	Clinical diagnosis	Aspiration biopsy (cell height in microns)	Regular section height in microns)	Diagnosis from aspiration biopsy	Diagnosis from regular section	Pathologic diagnosis
1. S. C.	59	M	Cardiac decomp., tremor	Large nodular	70-120	130/80	50	+54, +60	..	84	Yes	Loss	Toxic adenoma	9.5	8.8	T.N.G.†	T.N.G.†	Toxic adenoma
2. M. B.	23	F	Exophthalmos, cardiac murmur, sweats, tremor	Small	80-100	130/60	70	+68, +23	260	90	Yes	Loss	Diffuse toxic hyperthyroidism	8.1	8.3	T.D.G.	T.D.G.	Quiet phase, T.D.G.†
3. A. C.	33	F	Tremor, fatigue, palpitation, sweats	Large smooth	88-112	114/82	52	+62, +47 +39, +14	160	63	Yes	Loss	Diffuse toxic hyperthyroidism	9.2	9.5	T.D.G.	T.D.G.	T.D.G.
4. N. L.	57	F	Tremor, sweats, fibrillation, nervousness	Large smooth	90-110	188/80	108	+47, +43	Yes	Loss	Diffuse toxic hyperthyroidism	8.3	8.4	T.D.G.	T.D.G.	T.D.G., thyroiditis
5. E. P.	43	F	Tachycardia, tremor, muscle pains	Small	80-130	130/70	60	+46, +19	100	61	Yes	Loss	Diffuse toxic hyperthyroidism	10.5	10.1	T.D.G.	T.D.G.	Moderate hyperplasia
6. C. M.	28	F	Nervousness	Small subser.	95-115	120/60	60	+16, +29	..	83	Yes	Loss	Hyperthyroidism	9.7	9.0	T.N.G.	T.N.G.	Cystic hemadenoma
7. B. M.	60	M	Syst. murmur, spells, coma (diabetic, morphine addict)	Large nodular	80-105	135/70	65	+30, +47 +27, +24	130	..	Yes	Loss	Hyperthyroidism	7.8	8.0	N.T.N.G.	N.T.N.G.	Cystic hemadenoma
8. C. R.	58	F	Nervousness, tremor	Small	80-100	135/70	65	+42, +36	140	86	Yes	Loss	Toxic hyperthyroidism	8.7	8.4	T.D.G.	T.D.G.	T.D.G.
9. R. L.	34	F	Palpitation, nervousness	Small	80-110	145/80	65	+54, +33	..	90	Yes	Loss	Diffuse toxic hyperthyroidism	9.8	9.7	T.D.G.	T.D.G.	T.D.G.
10. C. L.	30	M	Sweats, nervousness	Small	95-120	130/75	55	+44, +30	..	74	Yes	Loss	Diffuse toxic hyperthyroidism	8.3	7.6	T.D.G.	T.D.G.	Moderate hyperplasia
11. J. M.	31	M	Nervousness	Large nodular	75-100	120/75	50	+35, +19	130	80	No	..	Toxic adenoma	8.4	8.5	T.N.G.	T.N.G.	Toxic adenoma
12. E. S.	44	M	Nervousness	Small	80-110	140/80	60	+34, +15	..	75	Yes	Loss	Hyperthyroidism	7.1	7.0	T.D.G.	T.D.G.	T.D.G.
13. E. C.	36	F	Exophthalmos	Small	85-120	140/85	55	+40, +23	..	80	No	..	Toxic adenoma	8.4	8.4	T.N.G.	T.N.G.	T. adenoma
14. S. T.	38	M	Sweats, nervousness	Large nodular	70-110	130/80	50	+56, +40	..	75	Yes	Loss	Toxic adenoma	8.7	8.8	T.N.G.	T.N.G.	T. adenoma
15. N. T.	57	M	Palpitation, sweats	Large smooth	90-110	116/62	54	+47, +38	110	61	Yes	Loss	Diffuse toxic hyperthyroidism	7.4	7.6	T.D.G.	T.D.G.	T.D.G., thyroiditis
16. F. R.	60	M	Fatigue, nervousness	Small nodular	95-115	128/64	64	+30, +25	100	65	No	..	Toxic adenoma	8.3	8.3	T.N.G.	T.N.G.	Toxic adenoma
17. H. W.	50	M	Palpitation	Small	84-96	120/70	50	+25, +18	..	54	No	..	Hyperthyroidism	7.8	8.0	T.D.G.	T.D.G.	T.D.G.

* Normal peak value of galactose tolerance is 30 or less in 1 hour.

† T.N.G. is toxic nodular goiter; T.D.G. is toxic diffuse goiter; N.T.N.G. is

nosis of toxicity was established. In 1, Case 7, the diagnosis of toxicity could not be established by aspiration biopsy. This patient was a diabetic and a narcotic addict which may explain some of the discrepancy.

The clinicians in charge of these cases used the basal metabolic rate, primarily for diagnosis, giving us, therefore, elevated B.M.R. readings in all cases. As we used only operated cases for these studies of aspiration biopsy we cannot draw a true comparison between the results of the 2 tests.

In 8 cases we obtained a blood cholesterol reading. Using a normal of 150 to 180 mg. per 100 cc., only 6 of the 8 were decreased enough to indicate a diagnosis of hyperthyroidism.

TABLE 2.—NORMAL CASES

	1	2	3
Patient	L. de F.	C. L.	G. W.
Age	24	22	25
Sex	M	M	M
Size of gland to palpation	Small	Small	Small
Average pulse range	65-80	75-82	70-80
Average blood pressure	104/80	120/80	120/82
Average pulse pressure	24	40	38
Basal metabolic rate	-2	+4	+2
Aspiration biopsy cell height, microns	6 7	6.3	5.3
Diagnosis as to function of thyroid gland from aspiration biopsy	Normal	Normal	Normal
Clinical diagnosis	Inguinal hernia	Postoperative appendectomy	Fractured femur

In 15 cases galactose tolerance tests were done. Using a normal peak value of galactose tolerance as 30 mg. per 100 cc. or less in 1 hour, we found that all 15 cases had readings indicating hyperthyroidism.

In all cases the presence of toxicity was confirmed by other clinical data and examination of surgical specimens in the ordinary manner.

Aspirations done on 3 normal cases likewise confirmed the accuracy of the test and helped confirm the standards for cell heights used as our criterion for diagnosis (Table 2). These aspirations again were of the magnitude expected. The average cell heights were all under 7 microns as would be expected in normal cases.

Summary and Conclusions. 1. A method has been described for obtaining aspiration biopsies of the thyroid gland.

2. Aspiration specimens from 20 thyroid glands were examined microscopically and 100 acinar cells measured from each. Surgical specimens from 17 of these glands were obtained and 100 acinar cells measured from each. These results were compared with each other and with clinical data.

3. It was found that a diagnosis of toxicity could be made on 16 of the first 17 aspiration specimens by the measurements alone. It was also found that measurements from the aspirations agreed very closely with those from the surgical specimens.

4. In the cases described, the measurement of acinar cell heights of thyroid aspiration specimens has confirmed the diagnosis of toxicity in a majority of cases. Though it is recognized that methods now

in use are often adequate to decide the matter of toxicity, it is hoped that this direct method may prove to be a valuable adjunct in the diagnosis of thyrotoxicosis.

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COLD HEMAGGLUTININS IN PRIMARY ATYPICAL PNEUMONIA AND OTHER RESPIRATORY INFECTIONS*†

BY THE COMMISSION ON ACUTE RESPIRATORY DISEASES‡

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UNTIL recently, autohemagglutination in man has been considered to be an unusual phenomenon, associated primarily with hepatic involvement or blood dyscrasias. In 1918, however, Clough and Richter¹ reported the finding of an autohemagglutinin in the serum of a case of bronchopneumonia. Their careful investigation revealed that the reaction depended solely on a peculiarity in the serum, occurred only in the cold, and was reversible at room temperature. The agglutinin was absorbed from the serum by the patient's cells and by human group O cells, as well as by cells of different species of animals. Although

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the agglutinating activity of the serum decreased as the patient recovered, it did not completely disappear. The conclusion was reached that the phenomenon was an individual and probably hereditary peculiarity, and that the strength of the reaction may or may not have been related to the acute infection.

During the past year, Peterson, Ham and Finland⁷ and others^{6,8,9} have noted the presence of cold hemagglutinins in the serum of patients with primary atypical pneumonia. In retrospect, it seems likely that the patient studied by Clough and Richter suffered from atypical pneumonia, and that the hemagglutinin was in all probability related to that illness. Knowledge of the mechanism of cold hemagglutination, however, has not been extended beyond that derived from Clough and Richter's study, nor have sufficient data been accumulated regarding the extent of the reaction in respiratory diseases.

The purpose of this report is to present the results of a study of cold hemagglutination in 93 cases of primary atypical pneumonia and 121 cases of other types of respiratory disease.

Methods. *Selection of Patients.* All of the patients included in this study were soldiers admitted to the Station Hospital at Fort Bragg during the winter and spring of 1942-43. The diagnoses were made by members of the Commission on Acute Respiratory Diseases and were based on the criteria presented in a previous paper.³ Patients were included in the study group if the diagnosis on admission was "probable atypical pneumonia," exudative tonsillitis, or exudative pharyngitis. Patients who had been ill for longer than 48 hours before coming under observation were admitted to the study only if the histories appeared to be reliable. Cases which were originally diagnosed as "probable atypical pneumonia" or exudative pharyngitis or tonsillitis, but did not eventually prove to be such, were kept in the series and studied in the same manner as the other patients. The final diagnosis and the number of cases in each category are listed in Table 1.

TABLE 1.—DISTRIBUTION OF 214 CASES BY DIAGNOSIS AND MAXIMUM COLD HEMAGGLUTININ TITER

Diagnosis	Maximum titer											Total
	<8	8	16	32	64	128	256	512	1024	2048	> 2048	
Atypical pneumonia	42	8	7	7	5	4	4	7	3	4	2	93
Pneumococcal pneumonia	2	2										4
Bronchitis resembling atypical pneumonia	8	2		1								11
Sinusitis	1											1
Exudative pharyngitis and/or tonsillitis	62	22	4	5		1						94
Scarlet fever	3		1									4
Measles	2		1									3
Undifferentiated	4											4

Figures in table indicate number of cases

Handling of Serum Specimens. Blood was taken from each patient when first seen, and thereafter 2 or 3 times weekly for the duration of his hospital stay. In most instances the final blood was taken about 1 month following onset of illness.

The blood was allowed to clot overnight at room temperature before the serum was removed. The serum was then stored in rubber-capped sterile bottles at 4° C. until used.

Technique of Test. All of the sera from each patient were tested on the same day. Human defibrinated Group O erythrocytes were obtained daily from the same donor for all tests. The cells were washed three times with approximately equal volumes of buffered physiologic saline⁴ and then packed in the horizontal centrifuge at 1500 r.p.m. for 15 minutes. A 0.2% suspension of packed cells in buffered physiologic saline was used in the test.

Two-fold serial dilutions of the sera beginning with a 1-4 dilution were made in buffered physiologic saline in 0.5 ml. volumes. To each of these was added an equal volume of 0.2% suspension; the final dilution of serum in the first tube was 1-8. After thorough shaking, the racks were kept at approximately 4° C. overnight. On the following morning the tests were removed from the refrigerator one rack at a time and read immediately before warming could occur. A fluorescent source of light and a black background were used. Readings were graded from 4+, which consisted of a tight disk of cells which did not break up readily on gentle shaking of the tube, to 1+, which was the least amount of definite clumping of cells visible to the unaided eye. The end-point was taken as the highest dilution in which definite agglutination occurred. Positive tests were reread after 30 minutes at room temperature to eliminate hetero-agglutinins or other antibodies as the cause of agglutination. All titers mentioned are final dilutions of serum and are expressed as the reciprocal of that dilution.

Positive sera of previously determined titer were included in each day's tests as a check on the sensitivity of the tests from day to day. In no instance did these control sera vary more than ± 1 dilution on repeated tests.

Results. Effect of Variations in Technique. The above outlined method was the final form of the test employed in this study. Before it was adopted, however, 317 sera were tested using the method described by Ham,⁵ in which a 2% suspension of cells was used. The change to an 0.2% suspension was made in the hope of increasing the sensitivity of the test. The results using the two concentrations of cells are compared in Table 2. With but 4 exceptions the titers were higher using the 0.2% suspension, and 59 sera which had been considered to have titers less than 8 using the 2% cell method, were found to have titers ranging from 8 to 256.

TABLE 2.—COMPARISON OF RESULTS OF COLD HEMAGGLUTININ TITERS OBTAINED ON 317 SERA USING TWO DIFFERENT CONCENTRATIONS OF CELLS

Titer using 2% cells	Titer using 0.2% cells						
	<8	8	16	32	64	128	256
<8	238	27	11	9	3	7	2
8	1	2	2	2	1
16	1	1	1	1	..
32	1	..	1	2
64	1
128	1
256	1
512

Figures in table indicate number of cases

The age of the erythrocytes was also found to be a factor in the results (Fig. 1). Nine sera were tested daily for from 4 to 6 days using cells taken from a donor on the 1st day of the experiment. The results are shown by the solid lines in Figure 1. In two sera (A and B) in which the maximum titer was 32, the titer fell to less than 8 when the cells used reached the age of 3 and 4 days respectively. The titer of one other serum (I), the maximum titer of which was 64, fell to less than 8 on the 6th day. The titer of serum C showed a drop of 3 tubes on the 5th day and serum G showed a drop of 2 tubes on the 4th and 6th days. Thus in 5 of the 9 sera tested there was a drop of 2 or more tubes in those tests using cells which were 3 or more days old. In contrast to this is the fact that the same sera when tested with

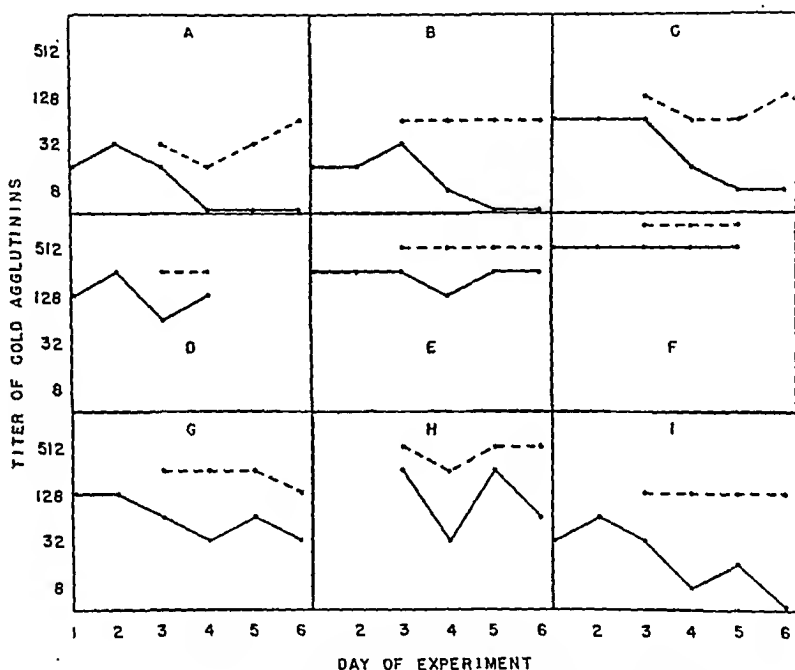


FIG. 1.—Comparison of cold agglutinin titers using cells obtained fresh daily (broken lines) and cells obtained on the first day and used throughout the experiment (solid lines).

fresh cells daily (broken line, Fig. 1) showed no tendency to a progressive decrease in titer, and the maximum variation was 2 tubes. In every instance, the tests performed with the fresh cells showed a much more definite and more easily read agglutination than did the same tests carried out with old cells.

In an attempt to evaluate possible differences in the agglutination of cells from different Group O donors, cells were obtained from 4 different donors and tested with 6 sera. There were no variations of more than 1 dilution in the titers.

Analysis of Cases. The results of the studies were analyzed for the purpose of determining the following points: (1) The titer of cold agglutinins in atypical pneumonia and other respiratory infection;

(2) the titer of cold agglutinins throughout the course of illness and convalescence; (3) the relationship of cold agglutinins to the severity of illness.

The Titer of Cold Agglutinins in Atypical Pneumonia and Other Respiratory Infections. Table 1 presents the maximum titers of cold agglutinins obtained during the illness in 93 cases of atypical pneumonia and 121 cases of other respiratory infections. The sera of 42 cases of atypical pneumonia had titers lower than 8. The remainder (51) had titers varying from 8 to more than 2048. In contrast, the titers for other respiratory infections studied range only from 8 to 32 with one exception. This single exception occurred in a patient ill with acute exudative pharyngitis. The maximum titer for cold

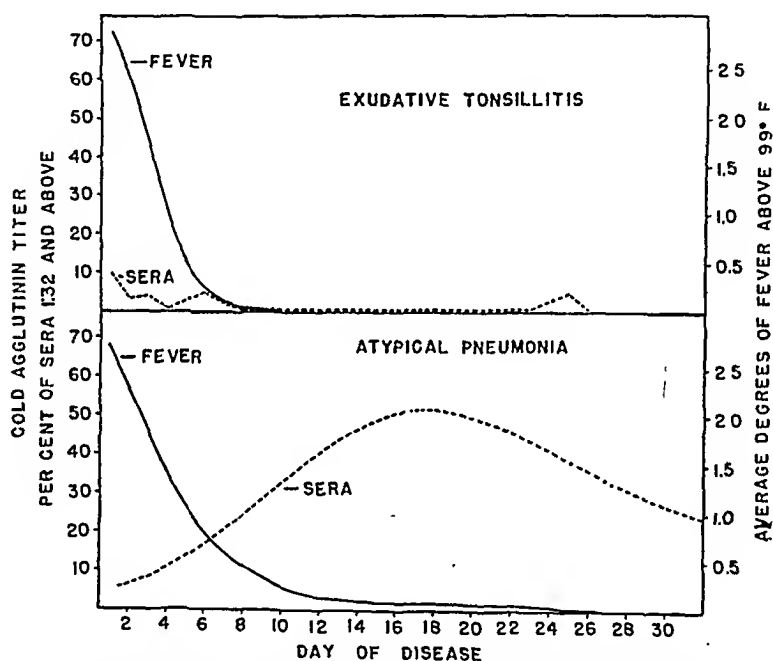


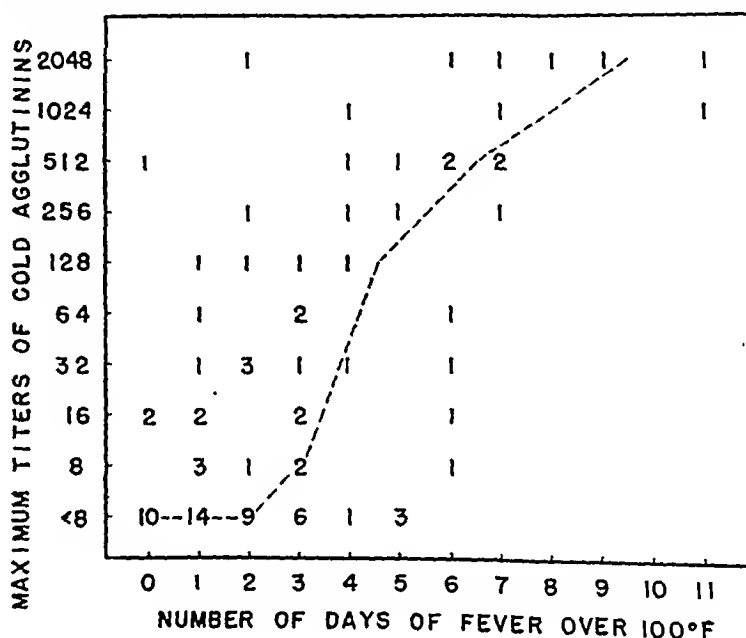
FIG. 2.—Percentage of sera from cases with atypical pneumonia and cases with exudative pharyngitis showing titers of 32 or more and average degrees of fever above 99° F. by day of disease.

agglutinins, which was 128, was found in the specimen obtained the day after the onset of his illness. Subsequent titers on specimens 4 days and 3 weeks later were 32 and 16, respectively. A Group A, non-typable, beta-hemolytic streptococcus was isolated from pharyngeal cultures, but the sera did not show a rise in antistreptolysin titer. There was no history of a recent antecedent respiratory infection. The explanation for the presence of cold agglutinins in this patient is not apparent.

Titer of Cold Agglutinins Throughout the Course of Illness and Convalescence. Figure 2 shows the per cent of sera from patients with atypical pneumonia and patients with exudative tonsillitis which had a titer of 32 or more by day of disease and compares this with the

average degrees of fever above 99° F. for each day. These data are based on 49 cases of atypical pneumonia and 85 cases of tonsillitis in which it was felt that the date of onset could be determined accurately. In the cases with atypical pneumonia the per cent of sera with a titer of 32 or more increased from 6% in the 1st week to 50% in the 3rd week of illness, at which time, if one considers the temperature curve as an index, the patients were well past the acute phase of their illness. The results in 85 cases of acute pharyngitis provide a distinct contrast when charted in the same manner. Ten % of the sera taken on the 1st day of illness showed a titer of 32 or more. Thereafter the incidence was never found to be above 5%.

TABLE 3.—DISTRIBUTION OF 89 CASES OF ATYPICAL PNEUMONIA BY NUMBER OF DAYS OF FEVER OVER 100° F. AND MAXIMUM TITER OF COLD AGGLUTININS



Relationship of Cold Agglutinins to Severity of Illness. Two objective criteria which lent themselves readily to reasonably accurate measurement were chosen as indices of severity of illness. These were the number of days of fever above 100° F. and the extent of the pulmonary lesion as evaluated by roentgenogram and physical examination.

Table 3 presents a correlation between the number of days of fever over 100° F. and the maximum titer of cold agglutinins at any time during the course of illness. The titer rose sharply between the 2nd and 10th days of fever. In general, the more days of fever which the patients experienced, the higher the cold agglutinin titer became. None of the cases with fever over 100° F. for 7 days or more had a titer lower than 256.

The relationship between the maximum titer of cold agglutinins and the amount of pulmonary involvement is shown in Table 4. Of

69 cases with single lobe lesions 22 or 32% had a titer of 32 or more, while of 18 cases with multiple lobe lesions 13 or 72% had a titer of 32 or more. There were 10 cases in which upper lobe lesions occurred either singly or in combination with involvement of other lobes. One of the 10 had a titer of less than 8; one had a maximum titer of 16, and the remaining 8 (80%) had titers of 32 or more. The highest titer seen in the entire series (65,536) had involvement of all three lobes of the right lung. The 3 cases with involvement of 1 upper lobe alone had titers of 8, 16, and 512.

TABLE 4.—DISTRIBUTION OF CASES OF ATYPICAL PNEUMONIA ACCORDING TO MAXIMUM TITER OF COLD HEMAGGLUTININS AND NUMBER OF LOBES OF THE LUNG INVOLVED

No. of lobes involved	Maximum titer cold agglutinins											Total
	<8	8	16	32	64	128	256	512	1024	2048	>2048	
1	37	5	5	5	4	3	2	4	2	2		69
2	2		2	1	1	1	2		1	2		12
3	1							3			1	5
4												
5										1		1

Figures in table indicate number of cases

It has recently been suggested by Dameshek² that the production of cold agglutinins might be influenced by the administration of sulfonamides. Sixty of the cases in this series are known to have received no sulfonamides during the course of their hospitalization. The titers in these cases ranged from less than 8 to 2048. Only 10 cases were treated with sulfonamides and the range of cold agglutinin titers was exactly the same as in the non-treated cases.

Discussion. During the last year numerous reports have appeared in the literature concerning the occurrence and significance of cold agglutinins in the sera of patients with primary atypical pneumonia. Peterson, Ham and Finland⁷ indicated that the presence of cold agglutinins might be of value in the differential diagnosis of this disease. They found that the highest titers occurred at or near the end of the febrile period. Horstmann and Tatlock⁶ confirmed these observations, and stated that they were unable to demonstrate a clear-cut correlation between the severity of the illness and the titer of cold agglutinins.

In the present series only 55% of the cases were found to have cold agglutinins and only 31% had titers of a level sufficiently high to distinguish them from other respiratory infections. Turner⁸ has reported a series from England of 22 cases of atypical pneumonia and 24 cases of other infectious diseases. Approximately 50% of the cases of atypical pneumonia in this series had titers of more than 16, whereas none of the other diseases had titers greater than 16. More

recently, Turner and others⁹ reported the results of a somewhat larger series of cases. They found that of 83 cases of atypical pneumonia, 50% had titers of at least 32 and 28% had titers of 128 or more. Of 136 cases of other types of disease including "influenza or grippe," undifferentiated upper respiratory infection, pulmonary tuberculosis and mumps, the titer was over 16 in only 4 cases and in no instance was it over 64.

The results reported here are in close agreement with regard to the percentage of positive titers with those of Turner and his co-workers^{4,5} but differ considerably from those of Peterson, Ham and Finland,⁷ and Horstmann and Tatlock,⁶ who reported that a large majority of their patients developed cold agglutinins. This may well be attributable to the fact that the present series and that of Turner *et al.* were both based on patients in military hospitals who, in general, may be less severely ill than patients admitted to civilian institutions. The data presented in Tables 3 and 4 suggest strongly that the height of the titer of cold agglutinins is related to the severity of the illness.

The data presented in Table 2 indicate that a titer of 64 or more in a patient ill with respiratory infection is strong evidence in favor of a diagnosis of atypical pneumonia. Lower titers are also of value, especially if sera taken at intervals during the course of illness show a rise in titer in early convalescence, and a drop thereafter. For example, in 93 cases of atypical pneumonia, there were only 8 cases with maximal titers of 32 or more which did not show this picture. The illnesses of 6 of these were of indefinite onset; in one a maximum titer was found 9 days after onset. In the 8th case, the maximum titer was found on the day after the estimated onset of atypical pneumonia. In this instance, however, the true onset was difficult to determine because of a mild respiratory infection which began 8 days earlier.

If the absolute level of titers is to be considered of value, it is important to know something of the limitations of the test used and the possible sources of error which may influence the results. Evidence has been presented to show that the age of the red cells used influences the sensitivity of the test. There is the further possibility that the test is subject to a certain amount of error because of possible variation in the agglutinating qualities of the donor's cells from day to day. It would appear from the data thus far obtained that variations in titer of one dilution in either direction may be expected with the methods employed.

Summary. 1. A modified method for detecting cold agglutinins in serum has been described.

2. A study of the occurrence of cold agglutinins in the sera of 93 cases of atypical pneumonia and 121 cases of other types of respiratory diseases has been presented and their value in diagnosis discussed.

3. In this series the titer of cold agglutinins was found to be proportional to the severity of the illness as measured by the number of days of fever and the extent of the pulmonary lesion.

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THE CONCOMITANT ADMINISTRATION OF SULFATHIAZOLE AND QUININE OR ATABRINE*

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In 1941 Harned and Cole² observed in rats that the concomitant administration of quinine and sulfapyridine increased the absorption of sulfapyridine from the intestine and also the percentage and total amount of the acetylated fraction in the urine. The largest dose of quinine used in their series produced an average increase of 96% in the excretion of acetylsulfapyridine. Since this effect was not accompanied by an increase in the volume of the urine, the possibility of renal damage suggested that these drugs should be considered, to an appreciable degree, therapeutically incompatible in the rat. The close relationship between the behavior of the sulfonamides in this species and in man inevitably raised the question of the existence in the human of similar incompatibilities. In malarial districts the frequent necessity for the concurrent administration of antimalarials and sulfonamides would appear to demand that the question be answered by observations on man, and because generalizations in this field are hazardous, conclusions drawn must be confined to the results from a specific combination of drugs.

The rather short life of sulfapyridine in therapeutics precluded its use in our human experiments. In its place sulfathiazole was sub-

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stituted. It is the purpose of this paper to report data on the concomitant administration of sulfathiazole and quinine or atabrine to 99 volunteer, hospitalized patients.

TABLE 1.—THE SCHEDULE OF DOSES

The sulfathiazole was given in 0.500-gm. tablets, the quinine bisulfate in 0.324-gm. capsules, the atabrine in 0.100-gm. tablets. When two drugs were administered on the same day a dose of each was always given at 8 A.M.

- Drug-Group 1. *Sulfathiazole*: 3 gm. daily for 7 days; 2 gm. initially followed at intervals of 8 hours by doses of 1 gm.
Quinine bisulfate: 1 gm. daily on days number 5, 6 and 7; 0.324 gm. per dose administered with the sulfathiazole.
- Drug-Group 2. *Sulfathiazole*: the same as in Group 1.
Quinine bisulfate: 1 gm. daily for the first 4 days; 0.324 gm. per dose administered with the sulfathiazole.
- Drug-Group 3. *Sulfathiazole*: the same as in Group 1.
**Quinine bisulfate*: 2 gm. daily for 7 days; 0.324 gm. per dose at intervals of 4 hours.
- Drug-Group 4. *Sulfathiazole*: 4 gm. daily for 7 days; 2 gm. initially followed at intervals of 6 hours by doses of 1 gm.
**Quinine bisulfate*: the same as in Group 3.
- Drug-Group 5. *Sulfathiazole*: 6 gm. daily for 7 days; 2 gm. initially followed at intervals of 4 hours by doses of 1 gm.
**Quinine bisulfate*: the same as in Group 3.
- Drug-Group 6. *Sulfathiazole*: 6 gm. daily for 6 days; the same schedule as in Group 5.
Atabrine: 0.300 gm. daily for 5 consecutive days; 0.100 gm. per dose at intervals of 8 hours. The administration of the atabrine started 24 hours before the first dose of sulfathiazole.
- Drug-Group 7. *Sulfathiazole*: the same as in Group 5. No antimalarial.

* In addition to the dosage recorded, 1 gm of quinine bisulfate divided into 3 equal doses was given during the 18 hours which immediately preceded the first dose of sulfathiazole.

Method. Of 76 patients who completed the experimental period, 9 were not included in the tables because they represented transitional doses of drugs or deviations from the adopted routines. The data on 67 subjects are recorded and analyzed. These were divided, according to the drugs and the daily doses, into 7 groups, Table 1. In general, the schedule called for the administration of sulfathiazole in daily doses ranging from 3 to 6 gm. for a period of 7 days. The daily dose of quinine varied from 1 to 2 gm. in the different groups and was administered during the last 3 days of the sulfathiazole-period in Group 1, during the first 4 days of the sulfathiazole-period in Group 2, and for 1 day preceding the sulfathiazole and then concomitantly with the sulfonamide for 7 days in Groups 3, 4, and 5. Atabrine was used in only one dose, 0.3 gm. per day for 5 days, and this drug was started 24 hours before the first dose of sulfathiazole (Group 6). A control group received only sulfathiazole for 7 days (Group 7). The first dose of sulfathiazole was given at 8 A.M. From this time throughout the experimental period, 24-hour specimens of urine were collected and analyzed quantitatively for free and total sulfathiazole. Each sample was examined microscopically for casts, cells and crystals. The specific gravity was determined and qualitative tests for albumin and sugar were made. If a patient discarded a specimen or vomited he was dropped from the experiment.

Twenty-eight hours after the first dose of sulfathiazole and at intervals of 48 hours thereafter, samples of blood were analyzed for free and total sulfathiazole, hemoglobin, and the total number of W.B.C. The method of

Bratton and Marshall¹ was used for the determination of sulfathiazole on filtrates of blood which represented a dilution of 1:100. Hemoglobin was determined by the Newcomer method.³ All colorimetric readings were made with a photoelectric colorimeter.

TABLE 2.—DIAGNOSES IN PATIENTS WHO COMPLETED EXPERIMENTAL PERIOD

Drug-Group Number: Mean age:	1 47	2 47	3 38	4 48	5 48	6 39	7 35	Total
Congestive heart failure	5	4	4	8	10		3	34
Inguinal hernia						6	2	8
Acute appendicitis						4	2	6
Lobar pneumonia	1		1		1			3
Amputation of both feet						1*	1*	2
Acute arsenic poisoning							1	1
Carcinoma of stomach			1					1
Incisional hernia							1	1
Head injury					1			1
Hodgkin's disease	1							1
Body and limb lacerations						1		1
Lung abscess				1				1
Pleural effusion					1			1
Neuritis			1					1
Trigeminal neuralgia			1					1
Pulmonary tuberculosis				1				1
Tuberculous lymphadenitis			1					1
Sciatica	1							1
Meningovascular syphilis					1			1
Total	8	4	9	10	14	12	10	67

* Same patient.

Subjects. Fifty % of the subjects were partially stabilized cardiac cases. Twenty % were surgical cases operated upon for hernia or appendicitis. The remaining patients were hospitalized for a wide variety of conditions, only 1 of which would have been expected to have yielded aberrant results. This was a convalescent case of acute arsenic poisoning, but the data on this patient were consistent with those of the other members of the group. Table 2 lists the diagnoses and mean ages of the patients in the 7 drug-groups studied.

Unfavorable Reactions. The patients were watched closely for subjective and objective evidence of toxicity. Of the 99 patients in the series, 5 were dropped for a lapse in coöperation, 1 undiagnosed case

was discontinued when there was no response to the experimental therapy, and 17 were abandoned because of unfavorable reactions to the drugs. Seventy % of the reactions consisted of vomiting, but most of these patients would have been continued had we not been interested in the quantitative relations between the intake and output of sulfathiazole. Vomiting appeared in each of the last 5 drug-groups, but the incidence in the groups which received sulfathiazole and quinine was about twice that in the groups administered sulfathiazole alone and with atabrine. The interpretation of this difference is complicated by the fact that the sulfathiazole-quinine groups contained a higher percentage of cardiac cases, and it is possible that the reaction might have been associated with changes in the heart produced by quinine or digitalis. The other unfavorable reactions were: mental confusion in 1 patient in Group 5; unexplained chills in 1 patient in Group 5; drug fever in 1 patient in Group 7; and hematuria in another patient in Group 7. This patient had a urine volume of 2400 cc. on the first day and 1890 cc. on the second day. The hematuria developed during the second day. Recurrent epistaxis was observed in 1 patient, in a transitional drug-group, who was receiving daily 6 gm. of sulfathiazole and 1 gm. of quinine bisulfate.

TABLE 3.—BLOOD SULFATHIAZOLE

Hours subsequent to the first dose of sulfathiazole												
Drug-Group	No. of patients	28					No. of patients	76				
		Sulfathiazole						Sulfathiazole				
		Free		Total		Free		Free		Total		Free
		mg. %	S.E.m \pm	mg. %	S.E.m \pm	%		mg. %	S.E.m \pm	mg. %	S.E.m \pm	%
1	8	3.2	0.14	5.5	0.42	57.7	8	2.5	0.39	3.8	0.51	66.5
2	4	2.9	0.26	4.2	0.17	69.4	4	3.3	0.22	4.9	0.39	66.6
3	9	2.6	0.36	3.4	0.42	78.0	9	4.0	0.30	5.5	0.48	73.4
4	10	3.7	0.49	5.0	0.67	75.0	10	4.0	0.70	5.6	0.99	71.6
5	14	5.1	0.65	6.5	0.63	77.9	13	4.5	0.64	6.9	0.74	64.2
6	12	5.4	0.26	6.6	0.34	82.0	12	4.9	0.27	6.2	0.26	78.4
7	10	5.3	0.59	6.8	0.61	78.4	10	4.9	0.40	7.4	0.35	66.2

Hours subsequent to the first dose of sulfathiazole												
		124						148				
		Free		Total				Free		Total		
		mg. %	S.E.m \pm	mg. %	S.E.m \pm	%		mg. %	S.E.m \pm	mg. %	S.E.m \pm	%
1	7	3.1	0.41	5.1	0.63	60.8	1	4.1	7.8	52.6
2	3	3.3	0.90	5.2	0.85	63.7	1	4.3	6.4	67.2
3	9	3.4	0.47	4.8	0.60	71.6
4	10	4.3	0.39	5.5	0.50	77.6
5	10	5.1	0.43	7.3	0.70	69.0	3	4.7	6.6	74.1
6	4	4.6	0.48	5.2	0.82	89.3	10	5.1	0.37	5.9	0.51	86.5
7	10	6.3	0.55	7.8	0.89	80.8

Results on Blood and Urine. Blood. Neither the hemoglobin nor the number of W.B.C. was affected unfavorably by any of the drug-combinations used. The sulfathiazole levels are recorded in Table 3. Neither quinine nor atabrine influenced significantly the free or the total sulfathiazole in any of the groups.

Urine. An inspection of Groups 1, 2 and 3 in which we have a combination of small doses of sulfathiazole with small and large doses of quinine reveals no effect of the latter drug on the total excretion of sulfathiazole or on the percentage excreted free (Table 4). However, when the dose of sulfathiazole was 6 gm. per day, quinine in daily doses of 2 gm. depressed the daily total excretion of sulfathiazole. The mean depression for the 7-day period of the ratio $\frac{\text{urinary sulfathiazole}}{\text{administered sulfathiazole}}$ amounted to 15%. Although the volume of urine in the group which received sulfathiazole alone averaged for the period more than that

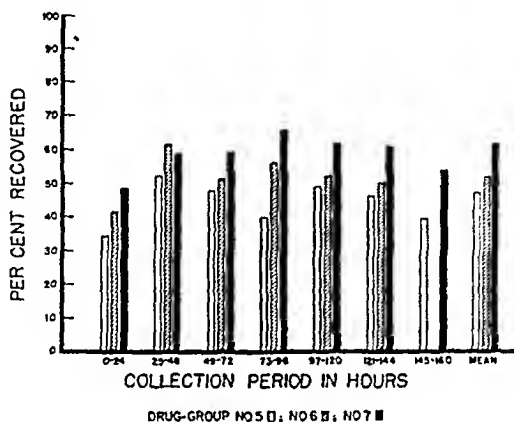


FIG. 1.—The effect of quinine and atabrine on the percentage of the administered sulfathiazole recovered in the urine. Drug-Group No. 5 received quinine and sulfathiazole; No. 6, atabrine and sulfathiazole; and No. 7, sulfathiazole alone. The dose of sulfathiazole was the same in each group. The complete schedule of drugs and the number of patients in each group are recorded in Tables 1 and 2.

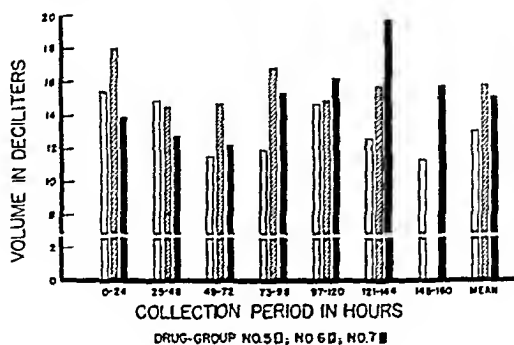


FIG. 2.—Urine volumes.

of the group administered the 2 drugs, the correlation between the urinary volume and the total amount of sulfathiazole in the urine is poor (Figs. 1 and 2). For most of the periods the concentration of sulfathiazole in the urine of the group administered quinine (No. 5) was less than in the control group (No. 7). It is also interesting to note that the percentage of urinary sulfathiazole excreted free is a little less in the quinine-group. This difference is not statistically significant, and as an isolated observation it would be unworthy of notice, but the same trend was observed in the results on blood.

TABLE 4.—SULFATHIAZOLE EXCRETED IN URINE
Hours subsequent to the first dose of sulfathiazole

[illegible]

Atabrine depressed the ratio, $\frac{\text{urinary sulfathiazole}}{\text{administered sulfathiazole}}$, to approximately the same extent as did quinine. In the atabrine-group the depression bore no relation to the urinary volume (Figs. 1 and 2). The percentage of free sulfathiazole in the urine was slightly greater in the atabrine group (No. 6) than in the control group (No. 7) and a similar tendency existed in the blood.

Summary and Conclusions. 1. The results obtained from 99 volunteer, hospitalized subjects indicate that the incidence of unfavorable reactions, with the possible exception of vomiting, is not increased by the concomitant administration of sulfathiazole and quinine or atabrine. The highest doses studied were: 6 gm. of sulfathiazole daily for 7 days; 2 gm. of quinine bisulfate for the same period; and 0.3 gm. of atabrine daily for 5 days.

2. The combination of drugs produced no detectible changes in the amount of hemoglobin or the total W.B.C. count.

3. Quinine and atabrine produced only minor changes in the free and total sulfathiazole in the blood and in the urine.

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THE EFFECT OF QUINIDINE ON THE MORTALITY OF RATS WITH EXPERIMENTAL MYOCARDIAL INJURY*

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THE action of quinidine on the normal heart has been the subject of considerable investigation by pharmacologists, and there seems to be general agreement that the chief effects are prolongation of the refractory period, slowing of conduction time, and decrease in contractility. Large doses may cause either auriculoventricular block or even sino-auricular block, while still larger doses may induce complete arrest or ventricular fibrillation. All of these effects are probably due to one fundamental action, namely, the decrease in the restorative metabolism of the heart as has been emphasized by Goodman and Gilman.² The paradoxical relationship between ventricular fibrillation and quinidine action, the latter tending at times to prevent and at times to produce the former, can probably be ascribed, as Smith, McEachern and Hall⁸ have pointed out, to the antagonistic effects of the action on conduction and on the refractory period. When the

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prolongation of the latter predominates the tendency toward ectopic rhythms is reduced. On the other hand, when the delay in conduction time predominates favorable conditions are set up for circus movements.

When we pass from the normal heart to a consideration of the abnormal heart there is less unanimity of opinion concerning the action of quinidine. The effects of the drug apparently depend a great deal on the state of the heart at the time it is given. Thus, Smith and Boland⁹ have pointed out that the drug causes sinus slowing in anesthetized animals and sinus acceleration in unanesthetized animals. Similarly, the prolongation of the P-R interval is much more striking in the presence of anesthesia, although the delay in intraventricular conduction occurs irrespective of anesthesia. The confusion which exists as regards the pharmacology of quinidine in abnormal hearts is reflected in the clinical literature. Most authors agree that the drug may be invaluable in the patients with ventricular tachycardia, but there is still considerable uncertainty concerning the indications and contraindications for it in patients with auricular fibrillation and in individuals who have a condition which is likely to lead to ventricular fibrillation. The suggestion has been made^{4,10} that the drug should be used routinely in patients with coronary thrombosis, in an attempt to prevent ventricular fibrillation and sudden death. This suggestion has received certain support from the experiments of Wegria and Nickerson,¹² who have studied the susceptibility of the hearts of dogs to ventricular fibrillation induced by electric shocks of various strengths. They found that in these animals quinidine reduced susceptibility to ventricular fibrillation, but only provided the dose of quinidine was not too large and provided it was administered slowly. When large doses were administered rapidly, the susceptibility to induce fibrillation increased and spontaneous ventricular fibrillation frequently occurred.

In order to simulate more closely in experimental animals conditions that occur in patients, certain investigators have studied the effect of quinidine in dogs following the ligation of a coronary artery. Mousset de Espanes⁵ observed no effect from quinidine in reducing the liability to ventricular fibrillation following such experimental coronary occlusion. On the other hand, Smith, McEachern and Hall⁸ reported opposite results. They produced occlusion of a large coronary branch in conscious dogs and observed that, although the animals receiving the drug were susceptible to ventricular premature beats and ventricular tachycardia, they exhibited a diminished tendency—as compared to the controls—toward the development of fatal ventricular fibrillation. The mortality in their experiments was 55% in the animals receiving quinidine as compared to 75% in the control group. However, only a relatively small series of animals was used.

One finding of especial interest, reported by Smith, McEachern and Hall⁸ was that in conscious dogs the administration of quinidine seemed to reduce the pain caused by occlusion of a coronary artery. This is in keeping with the observations of Proger and Minnich,⁶ and of

Riseman and Brown,⁷ who found that the amount of exercise required to induce anginal attacks was increased by the administration of quinidine. It would seem that these interesting observations merit further investigation.

The problem as to the possible value of quinidine in preventing ventricular fibrillation in patients predisposed to it can only be solved by the study of a large series of well-controlled cases. In view of the variability of the response of different individuals to the drug, it seems likely that such an investigation would necessarily involve several hundred patients. Consideration of the expense involved in experiments on many scores of dogs likewise make it difficult to arrive at an answer in these animals. Consequently, we have chosen to attack the problem in rats, which offer the advantage of making it feasible to carry out investigations on a large number of animals at a relatively slight expense. The rat, however, suffers from the disadvantage that one cannot readily induce a condition strictly comparable to coronary thrombosis in man.

Experimental Procedure. All experiments were carried out on rats of either sex weighing approximately 200 gm. The animals were obtained from our own colony, which is a mixture of the Wistar and several other strains. Myocardial injury was induced by burning the ventricular surface of the temporarily exteriorized heart, according to the technique described by us elsewhere.¹¹ The amount of tissue injured was kept reasonably constant in the different rats, and hence it is believed that the degree of injury produced in the animals treated with quinidine is quite comparable to that in the controls.

In one series of animals, quinidine was administered intraperitoneally immediately prior to the operative procedure. Another and larger group of animals received the initial injection of quinidine at the conclusion of the operation. The dose of quinidine employed varied from 0.005 to 0.002 gm. in different experiments. At the conclusion of the operation the animals which had received quinidine were placed in a cage which contained food to which quinidine had been added in such amount that each animal consumed approximately 0.02 gm. of quinidine per day. The control animals were treated similarly except that they received no quinidine at any time. The treated animals received the drug in the amount stated for a period of 3 weeks, at which time therapy was discontinued, as it was learned from experience that after this time all surviving rats remained in good condition except for an occasional one which would die of intercurrent disease.

The animals were observed at frequent intervals during the first few hours after the operation, and daily thereafter. Postmortem examinations were made in an attempt to determine whether death was the result of hemorrhage from the heart, infection in the chest, intercurrent disease such as pneumonia, or was unexplained. We were naturally particularly interested in those animals which displayed unexplained death, for it might reasonably be assumed that in these the development of cardiac irregularities such as ventricular arrest or ventricular fibrillation was concerned in the production of death.

Results. *The Operative Procedure.* Arrhythmias developed in most of the rats. The one most commonly observed was a sudden bradycardia which occurred in many of the animals when the heart was exteriorized. While the surface of the ventricle was being seared, sudden tachycardia of apparently ventricular origin (electrocardiograms were not taken) occurred in many of the animals. Ventricular fibrillation, lasting only 1 to 3 seconds occurred in about one-half of

them and was followed in each instance by prompt recovery. An attempt was made to estimate the comparative frequency and severity of these arrhythmias in the rats receiving quinidine, as compared to the controls. No significant difference was noted. No observations were made concerning arrhythmias after the chest had been closed.

The operative procedure resulted in severe respiratory distress. The animals had to be first anesthetized deeply with ether before the chest could be opened. The procedures of opening the chest, exteriorizing the heart, searing the surface of the ventricles, replacing the heart in the chest, and closing the chest ordinarily required a period of 30 seconds to 2 minutes, during which respiration was almost totally ineffective. Consequently, many of the animals developed respiratory failure and did not breathe spontaneously when the chest was closed. Artificial respiration was given both by inflating the lungs through a tube placed tightly over the nose and mouth of the animal, and by pressure on the chest wall. Even so, a number of the rats could not be made to breathe following the operative procedure. The incidence of such respiratory failure was much higher in animals receiving quinidine than in the controls. This point will be emphasized in more detail later.

TABLE 1.—EFFECT OF PREOPERATIVE AND POSTOPERATIVE ADMINISTRATION OF QUINIDINE ON MORTALITY CAUSED BY BURNING THE MYOCARDIUM

Group	No. of animals	Operative deaths*	Postoperative deaths†	Deaths during 1st wk. (2nd to 7th day)	Deaths during 2nd and 3rd wks.	Survivors (after 3 wks.)	Mortality (%)‡	Remarks
I { Controls	30	3	4	7	0	16	40.7	Quinidine administered prior to operation
I { Treated ¶	30	2	12	4	1	11	60.7	
II { Controls	50	4	6	9	1	30	34.8	Quinidine administered after operation
II { Treated §	47	4	8	4	1	30	30.3	
III { Controls	25	0	0	0	1	24	4.0	Received quinidine then etherized; no operation
Total . . .	182	13	30	24	4	111		

* Under this heading are listed deaths due to the anesthetic and to hemorrhage from the heart.

† This includes deaths not due to hemorrhage and occurring within the first postoperative day.

‡ In calculating mortality the operative deaths were omitted from consideration.

¶ These animals each received quinidine, 0.01 gm. intraperitoneally, immediately prior to the operation, followed by 0.02 gm. daily orally, thereafter.

§ These animals received quinidine in similar dosage except that the intraperitoneal dose was given immediately after the operation.

The complete data of mortality are shown in Table 1. One can note here a definite discrepancy between the experiments in which quinidine was given preoperatively and those in which it was administered after the operation. It is clear that the administration of the drug prior to opening the chest resulted in a definitely higher mortality than was observed in the controls. It can be noted that this increase in mortality occurred almost entirely in the immediate postoperative period. (The term "postoperative" is here used to include all deaths from the time the chest wall was closed until the next morning.) Most of

the deaths so listed occurred immediately after closing the chest and were due to failure of the animals to breathe. In a few instances respiration began and then ceased within the next hour or two. The difference between the controls and the treated animals in regard to postoperative mortality was so striking that it could hardly have been due to chance. On the other hand, the mortality was somewhat greater during the subsequent period in the controls than in the animals receiving the quinidine. At the end of 3 weeks the total mortality was 40.7% of the controls and 60.7% in the animals receiving the quinidine, the difference being due to the greater incidence of the immediate postoperative deaths in the latter group.

When, on the other hand, the quinidine was administered postoperatively, *i. e.*, after the animal had recovered from the respiratory failure induced by the ether and the thoracotomy, the results were different. Here the mortality was slightly less in the animals receiving quinidine, but the difference between the two groups was so slight as to be of questionable significance.

In order to determine whether the doses of quinidine were in themselves toxic, additional control observations were made. Twenty-five rats were given intraperitoneal quinidine comparable to that received by the experimental animals, and were then subjected to ether anesthesia without an operation being done on the chest. Of these 25 animals, all survived the immediate procedure, and only 1 died in the following 3 weeks, this animal dying of intercurrent disease. It may therefore be concluded that quinidine in the amounts employed is not seriously toxic for normal rats.

At the beginning of the experiments, we had expected that if quinidine had any protective value this would be most pronounced if the drug were given preoperatively. However, the results mentioned indicated that this assumption was quite erroneous. The drug appeared to be harmful on preoperative administration and was either ineffective or slightly beneficial when given postoperatively. Observation of the animals indicated, as mentioned, that the increased mortality in those rats receiving quinidine preoperatively was due mainly to difficulty in establishing respiration immediately after closing the chest. Since inspection of the tongue indicated serious anoxia in practically every animal, it was thought that the increased mortality in the animals receiving quinidine preoperatively might have been related in some way to the combined effect of anoxia and quinidine. Accordingly, a series of experiments was done to test this point.

Animals were placed in glass jars and subjected to reduced barometric pressure (see Table 2). Of 13 control rats not receiving quinidine, 5 died from the effects of anoxia. Of 13 rats receiving quinidine, 3 died from exposure to a comparable degree of anoxia. The series is too small to justify the conclusion that quinidine tended to protect the animals from the effect of anoxia, but it does indicate that the drug did not make the animals more susceptible to death from anoxia. Another point of interest is illustrated by these experiments. It was found, as would be expected, that animals subjected to myocardial

injury a short time before, were decidedly more susceptible to the effects of anoxia than were normal animals.

TABLE 2.—EFFECT OF QUINIDINE ON SENSITIVITY OF RATS TO ANOXIA

Condition of rats	Duration of exposure to anoxia (min.)	Barometric pressure (mm. Hg)	Control rats		Rats receiving quinidine*	
			No. of animals	Deaths	No. of animals	Deaths
Normal	38	320	1	0	1	0
Normal	58	280	2	0	2	0
Normal	22	200	2	1	2	0
Heart seared 7 days before .	39	200	2	1	2	1
Heart seared 30 min. before .	30	280	6	3	6	2
Total	13	5	13	3

* These animals received quinidine sulfate, 0.01 gm. intraperitoneally, immediately before exposure to reduced barometric pressure.

Since the experiments indicated that oxygen deficiency could not be held accountable for the increased mortality in the series of animals receiving quinidine preoperatively, it was thought that the anesthesia might in some way be responsible. Induction of anesthesia by ether, the anesthesia being severe enough to allow one to operate on the chest, did not result in a significant mortality, for, as mentioned, 24 of 25 such animals which also received quinidine survived, a single death being due to intercurrent disease. However, in these experiments the degree of anesthesia did not proceed to respiratory failure, while in the animals subjected to myocardial searing, respiratory failure occurred in a large percentage; because in addition to the ether anesthesia, these animals had their chests opened for a period of $\frac{1}{2}$ to 2 minutes. Consequently, it was thought that a deeper degree of ether anesthesia, proceeding to the point of respiratory paralysis, might throw some light on the toxic effect of quinidine. Accordingly, the following experiments were done:

TABLE 3.—EFFECT OF QUINIDINE ON RECOVERY FROM RESPIRATORY PARALYSIS INDUCED BY ETHER

Duration of apnea,* (sec.)	Controls		Quinidine	
	No. of animals	Deaths	No. of animals	Deaths
15	1	0	1	0
20	3	0	3	1
25	4	1	5	1
30	5	2	4	1
35	2	1	2	0
40	18	3	18	12
Total	33	6	33	15

* This denotes the interval between cessation of breathing—induced by ether—and the institution of artificial respiration.

Sixty-six rats were placed in ether jars and kept there for varying periods following the onset of apnea. Half of these animals had been given quinidine—0.02 gm. per rat, intraperitoneally—prior to the induction of anesthesia. The experiments were quite convincing.

Of the 33 control animals, only 6 succumbed, while of the 33 animals receiving quinidine prior to the induction of respiratory failure by ether, 15 succumbed (Table 3). It therefore seems clear that the increase in mortality in the animals which were treated with quinidine prior to the operation on the heart, can be ascribed to the effects of this drug, in tending to cause fatal respiratory paralysis. This conclusion is in keeping with the observations of Gordon, Matton and Levine,³ who observed in cats that death due to quinidine usually occurred as the result of paralysis of respiration.

The other point of interest in the studies is the possible significance of the fact that in the series of animals receiving quinidine postoperatively, the mortality was somewhat lower than in the controls. The difference in total mortality was slight, but if the first postoperative day was omitted from consideration the animals receiving the drug exhibited a decidedly lower mortality (Table 1).

Discussion. The data which have been presented seem to justify the following conclusions: (1) Under the conditions of these experiments, the administration of quinidine subsequent to the production of myocardial injury caused a slight decrease in mortality. (2) The administration of quinidine prior to the production of myocardial injury caused a significant increase in mortality, such increase being due to the effect of the drug on depressing the ability of the animal to recover from respiratory failure.

Caution is naturally necessary in attempting to apply the results of a study on animals to the problem of the use of quinidine in patients with coronary thrombosis. In the first place there is the species difference; in the second place the type of injury produced by burning the myocardium is not strictly comparable to that induced by occlusion of one of the coronary vessels. Consequently, in the following discussion, the opinions expressed are based not only on these experiments but on our own clinical observations, as well as on experience of others as available in the literature.

There appear to be certain definite *contraindications to quinidine*. Among these is the presence of heart failure. Thus, the recent study of Smith and Boland⁹ indicated that sudden death following quinidine administration is likely to occur when the drug is administered to patients with congestive failure and is very rare in the absence of this condition. These authors believed cardiac standstill to have been responsible for the instances of sudden death occurring in their series of patients. However, the observations on cats of Gordon, Matton and Levine,³ as well as those reported on rats in this communication, indicate another possible explanation. These studies show that doses of quinidine which are ordinarily harmless may favor the development of respiratory paralysis, provided the breathing is already seriously disturbed. Hence, it appears possible that a similar mechanism may operate to produce death from respiratory failure when the drug is administered to patients already having disordered breathing as the result of cardiac failure.

In regard to the possible dangers of quinidine administration, one

has to distinguish heart failure of long duration dependent on chronic myocardial disease and without a complicating arrhythmia, from heart failure of short duration dependent on acute myocardial injury and precipitated by an arrhythmia. Thus, a person progressing favorably after coronary thrombosis may develop congestive failure following the onset of ventricular tachycardia, and in such conditions the administration of quinidine may be life-saving because the drug may abolish the ectopic rhythm. Similarly, we have seen several patients who developed auricular fibrillation for the first time shortly after coronary thrombosis and who as a result of the tachycardia and the arrhythmia developed congestive failure. In such patients likewise the drug should be used. On the other hand, when the heart failure has not been precipitated by the arrhythmia and when it is of longer duration, it would seem that the administration of quinidine is dangerous.

Although our experiments did not seem to indicate any particularly greater incidence of bradycardia and block following the administration of quinidine, there is nevertheless ample evidence in the literature to demonstrate that the drug may aggravate a preëxisting auriculo-ventricular or intraventricular block. (There is very little evidence that the drug will produce block in persons who have no disturbance of conduction and, in fact, our results, having been obtained on the hearts of normal rats, support this conclusion.) It would seem that quinidine is contraindicated in patients who have either auriculo-ventricular or intraventricular block, or who have a condition which is likely to lead to such disturbances of conduction. Since these complications develop much more commonly in persons with posterior than in those with anterior infarction, one should be especially cautious in administering quinidine to patients with posterior lesions. In order to make the distinction with certainty it is necessary to take electrocardiograms, and as a rule it would seem unwise to give quinidine to a patient without a previous electrocardiogram.

Aside from the presence of congestive failure and of auriculoventricular or intraventricular block, there are certain other conditions which probably constitute contraindications for quinidine. One of these is long-standing auricular fibrillation. Although embolism following the reëstablishment of regular rhythm is probably much less frequent than has formerly been supposed—it did not occur in any of the 41 cases reported by Smith and Boland⁹—this complication nevertheless has been reported in the literature and we have seen one instance which was probably the result of quinidine administration. Furthermore, there are certain patients with auricular fibrillation in whom the drug increases the heart rate by causing a change in the mechanism to that of flutter. Such an occurrence is exceptional and should not mitigate against the use of quinidine when auricular fibrillation suddenly develops as a complication of coronary thrombosis, and when there are no other contraindications to its use.

When we turn from the contraindications to a consideration of the *indications for quinidine* in persons with acute myocardial injury the

situation is somewhat less confused. In ventricular tachycardia, which is not a rare complication of myocardial infarction, the drug may be of great value. In auricular fibrillation of recent onset, quinidine would seem to be reasonably safe, provided none of the contraindications which have been cited exist. The most common indication for quinidine in patients with coronary thrombosis would seem to be anterior infarction with frequent premature beats. There is evidence to support the assumption that patients with frequent ventricular premature beats are more likely to develop ventricular fibrillation than individuals in whom this arrhythmia is absent. We have repeatedly administered the drug under these conditions and have usually observed a prompt cessation of the extrasystoles. No untoward effects have been observed in any patient. The question as to whether quinidine should be given to individuals with posterior infarction and premature beats is a more difficult one and will probably not be answered by any generalization. If the extrasystoles are quite numerous and the patient presents no evidence of conduction defects, quinidine should probably be given. If, on the other hand, there are only occasional premature beats and definite evidence of auriculo-ventriculo-intraventricular conduction defects exist, the drug would seem to be contraindicated.

Auricular flutter is a rare complication of coronary thrombosis, but occasionally occurs. We have seen one patient in whom the rate could not be slowed by digitalis but quinidine caused a prompt reversal to the normal mechanism with slowing in rate. Auricular premature beats, of sufficient frequency as to be important, and paroxysmal auricular tachycardia are rare complications of coronary thrombosis. Neither of these arrhythmias respond particularly well to quinidine. On the other hand, nodal tachycardia occasionally occurs, and we have seen several instances in which this arrhythmia had been refractory to other means of treatment and has yielded promptly to adequate doses of quinidine.

Another problem which has been discussed by several authors is whether quinidine should be administered routinely to all patients with coronary thrombosis who present none of the contraindications. The purpose here, of course, is to try to prevent ventricular fibrillation and sudden death. On the basis of the available evidence, our own belief is that this should not be done because some of the patients with posterior infarction may later develop conduction defects as the result of the infarct, and such defects would increase the likelihood of catastrophes from quinidine. There still remains the problem as to whether one should give the drug routinely in patients with anterior infarction irrespective of the presence of any arrhythmia and in the absence of any contraindication. Our results on the rats with experimental myocardial injury, as well as the observations of Smith, McEachern and Hall,⁸ might be interpreted to support such a usage of quinidine. On the other hand, the difference in mortality in the treated and untreated animals was not great in our series, and the likelihood of toxic effects of quinidine would seem to be less in the previously

normal hearts of the animals than in the abnormal hearts of patients with coronary disease. Therefore, until further evidence is available it would perhaps seem wisest not to give the drug routinely to patients with anterior infarction, but to reserve its use for individuals with the arrhythmias which have been discussed and, except in the case of ventricular tachycardia, to withhold it when the contraindications which have been mentioned are present. Our data would suggest that the dangers from the use of the drug are greater during the first 24 hours after myocardial injury than at a later date when the protective action is apparently greatest.

Operations on the heart are becoming more common and will probably increase in frequency during the war. It has been suggested by Beck and Mautz¹ that the routine use of quinidine in patients subjected to operations on the heart might decrease the incidence of sudden death. Our experiments would suggest that, if the drug is to be used in such patients, it should be withheld whenever there is any well-marked dyspnea or when any respiratory disturbance is likely to develop as the result of the anesthetic or the operative procedure, because it seems that the existence of a disorder of breathing markedly increases the likelihood of respiratory failure and sudden death following the administration of quinidine. A similar procedure would seem to be wise in the case of patients subjected to thyroidectomy. Here quinidine has been sometimes used in order to try to prevent postoperative ventricular fibrillation. We have used it preoperatively in a number of such patients and have never seen any untoward results. However, in view of the increased mortality in our animals when quinidine was administered preoperatively, we believe that in thyrotoxic patients the drug, if employed, should be used after the operative procedure has been completed.

Summary and Conclusion. The effect of quinidine was studied on the mortality of rats subjected to experimental myocardial injury. The following results have been obtained: (1) When the drug is administered preoperatively, there is a definite increase in mortality. This increase has been shown to be related to the depressing effects of the drug on respiration. (2) When the drug was administered postoperatively, there was a slight decrease in mortality and an apparently significant decrease in deaths occurring after the first 24 hours. (3) The indications and contraindications for quinidine in patients with myocardial infarction and in persons subjected to operative procedures on the heart have been discussed. It is concluded that the available evidence does not favor the use of the drug routinely for such patients, and that if it is to be employed its administration should be begun after several days have elapsed following the onset of symptoms.

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PROGRESS OF MEDICAL SCIENCE

PEDIATRICS

UNDER THE CHARGE OF
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URINE ANALYSIS IN PEDIATRICS; TEN YEARS PROGRESS

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THE purpose of this Review is to survey those advances in urinalysis of the past decade which are of importance in the medical management of pediatric patients. Designed to be practical rather than academic, the survey has been deliberately limited to tests of substances within the scope of the average technician with the equipment found in most clinical laboratories. More difficult technical problems which need handling by specialized skills and apparatus, such as hormone measurements, vitamin assays and creatine and mineral balances, are ignored or given but passing mention. Omitted also are descriptions of the intriguing liver and kidney function tests—the hippuric acid excretion test, the inulin and diodrast clearances, the hexose tolerance tests, the pituitary concentration test, and the like. For completeness sake it has been necessary with some topics to refer to occasional scientific contributions made prior to 10 years ago.

The subjects discussed comprise: (1) proteinuria; (2) quantitative counts of urinary sediments; (3) melituria; (4) sulfonamides; (5) pigments; (6) findings in newborn and premature infants, and (7) other miscellaneous items.

1. **Proteinuria.** Traces of mucinous proteins can be demonstrated in all urines,^{112,155} if carefully looked for by refined techniques. This holds for both children and adults. For 5 normal boys 2 to 7 years of age having urines negative with 20% trichloroacetic acid, Wang and Wu¹⁵⁵ found a daily elimination 5 to 14.2 mg. The exact quantities varied from day to day and from child to child. Proteins of this sort escape detection in the routine precipitation tests, which are less highly sensitive and pick up only serum proteins when present.

Proteinuria Associated With Physical Activity. That violent exercise or physical activity will induce proteinuria is almost too well known to require comment, but 2 recent studies on subjects in the pediatric age group have been reported. Thirty-seven boys 7 to 13 years of age, were tested, after racing, by Nakagawa and Kawamo.¹¹⁴ Following short foot-races (40, 60, or 135 meters) proteinuria appeared in 2 boys; following a long race (1200 meters) proteinuria appeared in 35 of the 37. Parenthetically, glycosuria never was noted. Of 36 high school athletes, aged 16 to 18 years, tested after football practice, Preston¹²³ found protein, casts, red cells and leukocytes in the urine of 6. Preston followed the urines of

15 of these players through the football season, and found only 3 that never exhibited proteinuria after at least 1 game. The encountered concentrations of protein in the urine ranged from 0.5 to 6 gm. per 100 ml. After the playing season was over, the urines of all but 1 youth again became protein-free.

Febrile Proteinuria. Of 11 different diseases in 300 patients studied by Ehrström,⁵¹ pneumonia and influenza gave rise to proteinuria 10 times as often as did any of the others. Neither duration nor height of the fever appeared to be of influence. Ehrström concluded that the pneumococcus must play a somewhat specific rôle in causing kidney damage.

Intermittent Proteinuria. References to the many early studies on the frequency of so-called intermittent or postural or *orthostatic* proteinuria in childhood can be found in the paper by Calvin, Isaacs and Meyer³⁰ in 1926. Studies since that time on large groups of children have apparently not been reported.

The literature concerning the etiology of orthostatic proteinuria was recently reviewed by Young, Haines and Prince.¹⁶³ The chief theories as to its etiology were later listed by Prince:¹²⁴ (1) Increased lordosis of the lumbar spine causing mechanical obstruction to the renal circulation. (2) Decreased renal blood flow concomitant with the fall in pulse pressure in the upright position. (3) Vasomotor instability. (4) Subnormal constitutional development. (5) Reflection of a general lowered condition—asthenia, malnutrition, lowered vitality and resistance. (6) Imbalance of the autonomic nervous system. (7) Actual lesion of the renal substance, very mild in character, not demonstrable by ordinary methods. (8) Focal infection in some cases. Other names which have been used to describe the condition are benign, functional, growth, adolescent, physiological, intermittent and cyclic proteinuria.

Intermittent proteinuria is no longer interpreted as a sign of disease of the kidney. This conclusion is based upon accumulated clinical experience which can be summarized under 4 headings:

1. In otherwise normal individuals, intermittent proteinuria has a high rate of occurrence as compared with the relative infrequency of the nephritic disorders. On testing the urines of 50,000 British soldiers during World War I, MacLean,⁹⁷ after deductions for pus or spermatozoa and of those with "less than 5 mg. per 100 cc.," demonstrated an incidence of 2.2%. McLeod and Ameuille,¹⁰⁷ in 1916, encountered 263 positive (3.7%), in 7041 French and British troops. Of 2269 West Point cadets and officers, Ashburn¹⁰ found 360 (16%), with proteinuria. In 20,000 men entering the University of Minnesota, Diehl and McKinlay⁴² found an incidence of 1065 (5.32%). On reëxamination, approximately 75% of those who had had a trace on entrance were protein-free. Bashford¹⁴ examined, 25 years later, some 30 men who had shown proteinuria when 14 to 16 years of age, and found only 1 still with protein in the urine. Of 3642 students entering the University of Pennsylvania, Burden²⁷ found 949 (26%), positive 69.3% of these were negative on reëxamination. Blatherwick²¹ reported on the urine findings in 15,000 employees of the Metropolitan Life Insurance Company, a group representative of the general population in age and sex distribution and state of health; 91.6% were negative, 3.3% had about 10 mg. of protein per 100 ml. and 1.7% had 20 mg. or higher. Of 4500 male youths aged 14 to 17, examined in Vienna during 1932 and 1933 by Nowak,¹¹⁶ 624 (11.1%), had orthostatic proteinuria, whereas but 36 (0.8%), had chronic kidney disease. Calvin, Isaacs and Meyer,³⁰ found the incidence to be 60% in 189 poor children and only 5% in 331

children from a well regulated orphanage. They ascribed the higher rate to the poor hygienic surroundings, the poorer state of nutrition, and the many untreated foci of infection.

In Wolman's¹⁶² study of the admission urine specimens of 22,000 presumably healthy American men entering the U. S. Maritime Service, of 400 completely studied instances of proteinuria, 382 were found to be intermittent or "orthostatic," and only 8 were proven to be nephritic. In another series of 110 men with urines negative on arrival, 56% showed proteinuria at least once when tested 8 times in a 5-day period. This latter study demonstrates that the values reported for the frequency of proteinuria must be viewed as minimal when based upon single specimen determinations, since random specimens will often fail to uncover the disturbance.

2. Intermittent proteinuria displays a definite cycle in relation to age. Its incidence rises from the sporadic childhood level to reach a maximum during the years of puberty and adolescence, and then declines rapidly above age 18 to become negligible above age 25. Thus, in Lauener's⁸⁶ investigation on 5000 school children, there was found an incidence of 6.7% in 1246 children aged 6 to 7 years; of 27% in 1350 children 10 to 11 years; and of 38% in 2481 adolescents 15 to 16 years of age. The percentages at all ages were higher for girls than for boys. It should be pointed out the protein shown by most of the children was in trace amounts. Lee⁸⁷ noted, among Harvard freshmen of average age 18, that proteinuria occurred in about 5%; whereas, in upper classmen of average age 20, the incidence was 3.5%. Diehl and McKinlay's⁴² college freshmen were 5.32% positive; whereas MacLean's⁹⁷ soldiers, older in age, were but 2.2% positive. In Thorp and Wakefield's¹⁵² 100 Mayo Clinic patients with age range 4 to 47 years, 26 were 12 years old or less, 67 were between 12 and 30, and only 7 were 30 or over. In 64 cases collected by Young, Haines and Prince¹⁶³ from the Johns Hopkins Hospital files, the ages ranged from 9 to 39 years, the majority being between 14 and 18 years. In Wolman's¹⁶² series, the incidence among Maritime Service trainees was highest at age 16 and declined quickly in men but a few years older.

3. There are two principal differences in the urine findings between intermittent proteinuria and true nephritis: (a) In nephritis the excretion of protein is continuous rather than inconstant, regardless of posture or exercise.^{53,63} Occasional instances of mild chronic glomerulonephritis which are subclinical for years, and the nearly well patients convalescing from acute nephritis, seem to be the only exceptions to this rule. With such cases the proteinuria may usually be elicited by active work or lordotic posture,⁵³ though absent or slight when resting. Sometimes, too, a mild nephritic proteinuria can be made to clear transiently by the forcing of fluids or administration of alkali in large doses,^{63,108,121} though generally speaking proteinuria persists constantly in active nephritis. (b) In addition, erythrocytes and casts appear regularly in the sediment during nephritis. Even the above-mentioned exceptional mild or latent cases with inconstant proteinuria usually excrete an increased number of red cells or casts, to be detected by careful microscopy or quantitative procedures such as the Addis sediment count.^{3,4} Intermittent proteinuria usually gives rise to no abnormal microscopic findings.

4. Actual follow-up studies of individual cases have brought out the harmless and benign character of intermittent proteinuria. Thus, when Palmer¹¹⁸ tracked down, after 8 or more years, 35 former college students who had once had proteinuria, only 2 still exhibited traces in the urine.

Of 35 others who replied to a questionnaire, not one was having symptoms of renal disease. After an average interval of 7 years, 64 cases were re-examined by Thorp and Wakefield,¹⁶² and all but 1 were in good health. Of 18 others that had had persistent proteinuria with an orthostatic increase, only 2 showed renal disease an average of 7.7 years later; the urine of the other 16 had become entirely negative. Nor did any of Lee's⁸⁷ students with proteinuria develop nephritis over a 5-year observation period. Of 14 patients followed by Young *et al.*,¹⁶³ 4 were protein-free in 2 years, 6 in 3 years, 1 in 6 years, and 3 in 12 years. Evers⁵⁵ reported that, after 9 years, insureds of the New York Life Insurance Company who had had proteinuria without casts or other evidences of nephritis, showed no increase in mortality above normal expected levels. Similarly, Christiernin, Dublin and Marks,³⁴ in a survey of policies issued by the Metropolitan Life Insurance Company from 1925 to 1935, and studied in 1937 and 1938, found no unusual mortality in otherwise normal proteinuric individuals, though when the proteinuria had been associated with hypertension or obesity the mortality was much above normal expectation. MacLean⁹⁷ found the distribution of "trench nephritis" no higher among troops who had had a positive protein test earlier in the campaign than among those whose urine had been negative. Of the 22,000 men studied by Wolman,¹⁶² 27 cases of acute glomerulonephritis and 7 cases of acute pyuria developed subsequent to entry for training, but not one single instance came from the group of 400 individuals with proteinuria in the initial arrival specimens.

Thus, from the evidence tabulated above, it may be concluded that when careful study uncovers no signs of nephritis or other renal disease, particularly when the subject is young, simple proteinuria of the intermittent type should be interpreted as a temporary reversible dysfunction and not as a positive or potential state of disease.

Concentration of Protein. With kidney disease, as is well known, the excretion of protein may range from 5 gm. per 100 ml. of urine or higher. In nephrosis or severe nephritis down to the faintest detectable trace, 5 mg. per 100 ml., or even none at all in convalescent nephritic patients when recumbent. Similarly in benign intermittent proteinuria the range may be nearly as great, from faint traces to at least as high as 3 gm. per 100 ml.¹⁶² In urologic lesions, proteinuria is irregular and unreliable as a diagnostic sign. It is evident, therefore, that the magnitude of the concentration of protein in individual specimens of urine is of little aid as a definitive criterion for distinguishing among the various types of proteinuria. Viewed statistically, however, the *mean* values for the concentration of protein are of greater magnitude in patients ill with kidney disease than in subjects having benign proteinuria.¹⁶²

In this connection, one may mention the observations on adults with chronic nephritis by Berglund, Scriver and Medes.¹⁸ These workers found a temporary increase in protein elimination on the change from resting to active walking, and a more permanent rise after the change from a low to a high protein intake. They found, too, that the *rate* of protein excretion per hour remained about the same regardless of whether there was diuresis or a scanty highly concentrated urine. Hence, one cannot estimate the total daily excretion of protein from the amount in a single urine sample, without taking into account specific gravity and rate of diuresis. In acute nephritis, Berglund and Frisk¹⁷ noted that the rate of proteinuria is subject to quick inexplicable changes, irrespective of diet, particularly in the direction of improvement.

In intermittent proteinuria, as the name indicates, no constancy prevails. Urine specimens may be entirely protein-free at any time during the day as well as in recumbent inactivity. With many subjects, the assuming of a lordotic posture for an interval of time will not aggravate the protein elimination, though the majority do respond in this way.

Nephritis. Pathogenesis of Proteinuria. Though traditionally referred to as "albumin," urinary protein ordinarily consists of both albumin and globulin. The literature dealing with the nature and origin of the urinary proteins in renal disease was reviewed in 1936 by Bing,²⁰ to whose article the reader is referred for specific references. He pointed out that blood and urine proteins have been proved identical in chemical composition, in physical properties such as optical rotation, racemization, osmotic pressure and specific refraction, and in immunologic responses to precipitation, complement fixation and hemolysis reactions; on the other hand, proteins extracted from the kidney exhibit no such corresponding identity. Additional evidence that the urine proteins come from the blood is the lowering of the level of plasma protein in patients with proteinuria; it would seem impossible for the renal parenchyma to secrete such large quantities of protein as are excreted daily in severe proteinuria.

Moreover, the urine proteins are not abnormal plasma proteins removed as foreign bodies or as elements in a detoxication process. Bing emphasized that the diffusibility of the serum proteins is no greater in the proteinuria patient than in normal individuals. Intravenous injection into healthy animals or men, of either serum or urine protein from patients ill with nephritis, will not cause proteinuria. On transplantation of a healthy dog kidney to the neck of a dog having uranium nephritis, no protein will be excreted through this "neck-kidney," whereas similar transplantation of a uranium nephritis kidney to either normal or nephritic animals will be followed by proteinuria from this kidney.

The leakage of protein is greater in nephrosis and amyloidosis than in glomerulonephritis and nephrosclerosis. With all of these conditions, Bing found fairly constant values for protein excretion from day to day under constant conditions, though the quantity rose and fell parallel with the protein content of the diet, and there was a rise after acid ingestion and in fever. These variations were appreciable and not related to corresponding variations in the creatinine clearance. The more prominent the glomerular lesions, the greater the excretion of large moleculéd globulins. With cases having badly damaged glomeruli, as in beginning glomerulonephritis or late chronic glomerulonephritis with renal insufficiency, the ratio of albumin to globulin in the urine is low—between 3 and 10; conversely, in nephrosis, which has slight anatomic changes, the ratio becomes high, there being 10 to 20 times as much albumin as globulin. The very large molecule of fibrin is encountered but seldom in the urine. The foregoing statements from Bing's paper epitomize the current concepts of the genesis of the urine protein in nephritis. In the present Review the literature on the metabolic disturbances occurring in nephritis will not be touched upon.

The quantity of protein reaching the urine may not be dependent solely upon glomerular leakage, according to Addis,^{3c} who was interested in Walker and Oliver's¹⁵⁴ observation that an animal's glomerulus may leak protein up to 30 mg. per 100 cc. of glomerular filtrate. If a human subject lost but 20 mg. per 100 cc. in his usual 24-hour glomerular filtrate of 180,000 cc., the total excretion per 24 hours would amount to 36 gm. of protein. Inasmuch as actual excretions during proteinuria are much

lower than this amount, and in the light of suggestive experiments of Gérard⁶⁷ and Randerath,¹²⁶ Addis suggested that some tubular resorption of protein may take place in the human kidney.

In boys before puberty, proteins from the prostate or seminal vesicles will not appear in the urine after local massage of the parts, according to Calvin,²⁸ and therefore the proteinuria found in subjects of this age cannot be attributed to such substances.

2. Sediment Counts (Addis). A small number of formed cellular elements can usually be recovered from any specimen of normal urine if intensive search is made. It is the increase in the quantities of these elements which assumes importance as one of the cardinal attributes of the disease, nephritis. For quantitative enumeration of cells and casts, the method proposed by Addis^{3a,b} is in widest use. This technique counts all the red cells, leukocytes and casts which are passed in a 12-hour period. For best results, the patient should have a low fluid intake for half a day prior as well as during the test period and not be receiving alkali medication, in order that the urine when passed for collection be acid and not dilute. These precautions, plus a few drops of strong formalin placed in the collecting vessel, are essential to preserve the cellular elements from lysis, yet most laboratory manuals fail to so advise. Many published studies on results and interpretations of the test omit specific mention as to whether such measures had been taken in the gathering of their data. Since the sources of error are many, it is wise to do counts in duplicate.

Wide variations occur in normal subjects, and no close division can be drawn between normal and abnormal. As Addis^{3a} pointed out, the method is not strictly quantitative; its chief intent is to express the rates of excretion in terms of approximate magnitude. Fluctuations in specific gravity and urine volume are more likely to occur in childhood than in adults, according to Lyttle,⁹⁶ who recounted the difficulties in making children coöperate in the restriction of fluid intake for the necessary 24-hour period.

Normals. Most of the reports on record deal with adults. However, a few pediatric workers^{24,28,96,129,131} have commented most favorably on the usefulness of the Addis count for following the progress of recovery from acute nephritis. Before reviewing their findings, it is essential to have normal values clearly in mind. The upper limits of excretion for a 12-hour period in healthy children under 13 years of age, as compared with adults and expressed in round numbers, stated as follows:

<i>Author</i>	<i>No. of children</i>	<i>Casts</i>	<i>Erythrocytes</i>	<i>Epithelial cells and leukocytes</i>
Addis ³ (for adults)	5,000	500,000	1,000,000
Rew and Butler ¹²⁹	16	38,000	275,000	850,000 (boys) 4,000,000 (girls)
Lyttle ⁹⁶	74	10,000	600,000	600,000 (boys) 1,000,000 (girls)
Soto ¹⁴³	306	7,300	950,000	3,000,000
Boyle <i>et al.</i> ²⁴ (postnephritic children)	25	18,600	115,000	1,000,000

In nephritis the shedding of cellular elements into the urine becomes greatly increased, the magnitude of the sediment counts being from 2 to higher than 1000 above these upper normal limits.

Nephritis. Snoke¹⁴¹ listed several "compelling reasons" why the Addis concentration method is essential for intelligent diagnosis and prognosis in

cases of renal disease: (a) Preservation of the formed elements is satisfactory only by this method. Snoke cited instances with low specific gravity or alkaline reaction and no casts or R.B.C. in the routine specimens; yet the patients were ill with active nephritis and large numbers of casts and R.B.C. could be demonstrated by the concentration technique. (b) Exact measurement of the numbers of cells and casts excreted is more dependable than estimates made by ordinary techniques. Thus, one or two R.B.C. per high-power field seen in an ordinary test, may be regarded as having little significance, yet if the specimen is dilute this number may be representative of an excretion of several million cells per 12 hours—a significant figure. (c) No other method affords reliable comparison of the specimens with each other and the determination with reasonable accuracy of increase and decrease of formed elements. Fluctuations in dilution and hydrogen-ion concentration make the ordinary tests nearly worthless for quantitative recognition of changes for better or worse in renal lesions. (d) The Addis count is a more delicate test for renal disease than is the blood urea level, phenolsulfonephthalein excretion and other functional tests which often give normal values in the presence of mild or minimal nephritis. For example, Snoke was able to uncover 14 mild chronic cases of glomerulonephritis in one children's clinic by following up with the Addis test healthy appearing youngsters who had exhibited mild albuminuria, hematuria or casts in their preoperative routine urinalyses.

Rubin, Rapoport and Waltz¹³¹ found the red cells to be the most constant and persistent abnormality of the Addis count. Taking the value of 1,000,000 red cells per 12 hours as the upper limit of normality, these workers found that during recovery from acute glomerulonephritis there is a correlation between the return of the sedimentation rate and the red cell count, though the latter usually becomes normal about 5 weeks later than the sedimentation rate. In 40 children with acute glomerulonephritis, the routine urinalysis returned to normal on the 37th day, on an average, whereas the Addis count required 120 days to achieve normality. There was a close correlation between the number of days it took for the 12-hour R.B.C. excretion to drop to the 10 million level (70 days) and the time required for the sedimentation rate to become normal (86 days). In an 8-year experience they saw no recurrence of acute glomerulonephritis in any patient who had shown a complete recovery (by Addis count and sedimentation rate) following the first attack.

Other Diseases. In children with acute infections, Rew and Butler¹²⁹ found, by means of Addis counts, that the urine sedimentary elements tended to be more abundant than in control children free from infections.

Lyttle⁹⁶ performed sediment counts 3 times weekly on 14 cases of scarlet fever. His patients were males aged 4 to 14 years, kept in bed on a low protein-low salt diet. One had had scarlet fever 7 years previously, and another had had acute glomerular nephritis following tonsillitis (hemolytic streptococcus) a year earlier. None of the 14 patients developed clinical signs or symptoms of postscarlatinal nephritis, but every one showed a moderate transient increase in the excretion of protein and formed elements at some time between 8 to 45 days after onset of the scarlet fever. The highest levels reached (per 12 hours) were: for protein, 174 mg.; for casts, 1,320,000; for R.B.C., 12,915,000; for epithelial and W.B.C., 9,460,000. Lyttle's comment was that it is difficult to draw any definite line between these subclinical signs of renal irritation and true post-scarlatinal nephritis, though red cell excretion in an ordinary hospital case

of nephritis is usually in the hundreds of millions. On reviewing the medical literature, he found a number of other reports which, while not quantitative, showed that the great frequency of renal irritation in scarlet fever was already well known. Lyttle's studies confirm this indisputably, and emphasize that microscopic hematuria can be detected much more dependably by the Addis method than by routine urinalysis.

Orthotolidine. Orthotolidine (*not* orthotoluidine) is more sensitive and more dependable than guaiac or benzidine for the detection of blood in urine. This reagent, first utilized for detection of blood by Ruttan and Hardisty¹³² in 1912, was recommended for the detection of occult hematuria by Stone and Burke¹⁴⁵ in 1934. Barach and Pennock¹² found orthotolidine useful for this purpose. Its application to the pediatric problem of nephritis was explored and found satisfactory by Calvin and Carbone²⁹ and Weiner and Schwartz.¹⁵⁷ The test is simple to perform. To the centrifuged sediment of 15 ml. of urine resuspended in 1 ml. of urine are added 2 drops of 1% orthotolidine solution in pure methyl alcohol, and 2 drops of a mixture of glacial acetic acid 1 part and commercial hydrogen peroxide 2 parts. A transient blue color represents a positive result, the intensity of the color paralleling roughly the number of red cells present. Weiner and Schwartz compared the findings of the orthotolidine test with those of the Addis count in children recovering from acute nephritis. They secured positive results with the chemical test when the Addis red cell count was 17,250,000 or higher; they concluded that this test was not delicate enough to pick up low orders of pathologic excretion of red cells. In the Reviewer's experience, however, the threshold for positive reaction with orthotolidine is lower and more sensitive than the above value.

3. Melituria. The sugar most frequently found in children's urine is dextrose or glucose, but pentose, fructose, galactose, sucrose and more complex polysaccharides may be found at times. Most American workers restrict the term *glycosuria* specifically to dextrose, and apply *melituria* more broadly to designate abnormal excretion of any sugar in the urine. Melituria, as observed in adults, has been well surveyed in recent years by Bock,²² Cantarow and Trumper,³² Marble,¹⁰⁰ Reiner,¹²⁷ and others. The discussion which follows emphasizes those aspects which are of importance to the pediatrician, many of which have been ignored in the reviews planned for the internist.

It is an axiom of good pediatrics that any infant or child having persistent sugar in the urine be given a diagnostic study. Granting that diabetes in childhood is rare in comparison with the relatively great frequency of melituric reactions, there is always the possibility that the subject in question has the disease. Even when the condition turns out to be a benign glycosuria of alimentary, emotional or low renal threshold origin, or one of the less familiar meliturias, the information now secured will be of service in future years if the excretion of sugar persists or recurs.

Techniques for Recognition and Identification. It is important first of all to make sure that the performance of the urinalysis itself is free from technical error, since the tests for sugar are often not properly made. For the initial recognition of sugar, the widely used Benedict's qualitative copper reagent is superior to both Trommer's and Fehling's reagents, in that it gives fewer false positive reactions. It must be remembered that saccharose or sucrose is not revealed with these reduction methods. In urines containing 0.03 to 0.15% creatinin, which is the range occurring in the majority of human urines, the Benedict test has a threshold sensi-

tivity of about 0.05 %, or 50 mg. of sugar per 100 ml. of urine.¹³⁵ The minute quantities of dextrose and other reducing substances which escape normally into all urine specimens are of a lesser order of magnitude and will not be caught by this test. The roster of these other reducing substances comprises, among others, ascorbic acid, the glucuronic acids, uric acid, creatinin, di- and polysaccharides derived from dextrinous foods, and derivatives of salicylates or cinchophen when these are being taken by mouth. Reference to Benedict's¹⁶ original paper shows that the boiling time originally recommended for the test was but 1 to 2 minutes. Folin and McEllroy⁶⁵ have indicated that 3 minutes in a boiling water bath is equivalent to 2 minutes over a flame. The presence of excess reducing sugar will become manifest by that time.¹³⁵ For extreme accuracy, the reading should be made at once when the specimen is taken from the source of heat, and not after it has been kept standing hot for some moments longer. The 5-minute period instructed by most texts is too long, since reducing substances more slowly acting than the hexoses may then evoke false positive readings. When the qualitative test is positive, it should be followed by a quantitative reduction test to get a record of the concentration of sugar present.

When the urine test is positive, it is wise to attempt the identification of the contained sugar. Most laboratories will find it easiest to begin the identification by fermentation with baker's yeast. In the fermentation test, glucose and fructose will be destroyed; lactose and pentose will be untouched; galactose may break down a little. Castellani and Taylor³³ advised that special pure strains of yeast be utilized, but in practical experience ordinary commercial baker's yeast is dependable and satisfactory. After the fermentation, centrifuge or filter the urine to be rid of the yeast, then repeat the quantitative reduction test. The difference between the 2 quantitative determinations after allowing for dilution by the yeast emulsion represents the fermentable sugar. If the second determination shows that more than a trace remains unfermented, the presence of two different sugars is indicated, and then each must be separately identified.

Differentiation of fructose from glucose, both fermentable, if no polarimeter is available (and few clinical laboratories possess one), is effected by the Lasker and Enklewitz⁸⁵ technique of placing a mixture of urine and Benedict's qualitative reagent in a water-bath for 10 minutes at 50 to 60° C. Fructose, being a ketose, reduces quickly at this temperature, whereas glucose does not. One may apply also the Seliwanoff resorcinol test for ketoses or search for the insoluble methyl fructosazone. If the sugar is fermentable and the fructose tests negative, the sugar may be presumed to be glucose itself. For positive identification of glucose, if desired, prepare the osazone or measure the rotation of polarized light.

Of the non-fermentable sugars, pentose will give a positive reaction with Benedict's solution at 50° to 60° C. in less than 10 minutes, or when the mixture is left standing at room temperature for 3 hours or longer. The mucic acid test denotes galactose or lactose (these two can be differentiated by the phloroglucinol reaction). The Bial HCl-orcinol-ferric chloride test, the aniline-acetate reaction and that of Tauber¹⁵⁰ will indicate pentose. For lactose the Rubner test is insensitive and misleading, according to Edson;⁵⁰ the phenylosazone technique is best. The osazone tests, generally speaking, are very helpful when clear-cut, but unfortunately many urines contain mixed sugars and give rise to atypical complex crystalline forms. For critical description of these and more technical

methods, the reader is referred to standard texts on biochemistry, to Hawk and Bergeim's⁷⁶ "Physiological Chemistry," to Reiner's "Manual,"¹²⁷ and to Edson's constructive comments.⁵⁰

Differentiation and exact identification of the sugars requires experience. It may be necessary to check the procedures themselves by control tests with known sugars added to urine, while realizing that commercial preparations of the individual sugars themselves are not always wholly pure. In practical work, the fermentation and temperature reduction reactions may be as far as one is able to go, leaving the more specific and difficult tests to specially interested laboratories.

Exton⁵⁶ has stressed that it is unsafe to assume that glucose, or indeed any other sugar, is the cause of a positive reduction test, especially when concentrations run 1% or less. He devised an ingenious method for identifying the various reducing substances, applying the universal Electro-Scopometer to the measurement of their distinctive reduction rates when mixed with a di-sodium-di-nitro-salicylate reagent. His studies emphasize the motley variety of non-glucose reducing substances which may appear in urine, and the importance of the as yet unexplored field of the urine sugar mixtures which are often unexpectedly met.

Reference may be made in passing to the new powder reagents which have lately been developed for the rapid detection of sugar in urine.^{73,144} Consisting essentially of bismuth salts already mixed with other reagents, these powders, commercially available, change color in the presence of reducing substances. They require almost no equipment and are stated to be accurate and selective.

Most children when in good health can ingest an abundance of carbohydrate without developing alimentary glycosuria. In an unpublished study of the 1-hour 2-dose glucose tolerance test (Exton-Rose) in childhood, Du Swun Deh⁴⁸ found, with 90 youngsters ranging in age from early infancy to 11 years, that 2 test doses of 1.75 gm. per kilo body weight given after an overnight fast did not in any instance spill into the urine to give a positive reduction test.

Alimentary Melituria. Any of the sugars, if fed in inordinate amounts, will overflow into the urine. Thus fruits or fruit juices when taken in excess gives rise to pentosuria or fructosuria, occasionally in combination; cane sugar produces sucrosuria or glycosuria; candy induces glycosuria, maltosuria or dextrinuria; excess lactose or galactose result in lactosuria or galactosuria. Alimentary meliturias of this sort, of dietary origin, are transient and harmless. They are seen most often during febrile illness because fruit juices and other carbohydrate-rich foods are forced at a time when the physiologic functioning of the small intestine and liver is not at its best, and because urinalyses are commonly done at these times. Hospitalized patients, while receiving glucose solutions by vein, usually have glycosuria. Folin and Berglund⁶⁴ have described the escape into the urine of appreciable amounts of dextrin derivatives following the ingestion of dextrans and caramelized starchy foods. Foods containing pentosans—among them, grapes, cherries, strawberries, blackberries, prunes, wine, fruit juices and fruit-flavored soft drinks and beer—can provoke a transient excretion of xylulose or arabinose into the urine.

The transient character of such melituria in children is brought out by Mihara.¹¹⁰ Of 1648 children, the incidence of specimens positive for reducing substances was as high as 5.8%. Unfortunately, the only available summary of Mihara's paper, that of Kato, fails to give the state of health of these children, but the high frequency of positive reactions and asso-

ciated acetonuria implies that the specimens were collected in a hospital for sick children. On osazone identification, glucose was found to occur most frequently (86%), the other sugars being lactose, galactose and maltose. The incidence of positive specimens was higher in the younger age groups, and during the summer months. Acetonuria was nearly as common as melituria. No significant relationships were noted between dietary habits or types of disease and melituria. Sugar tolerance tests on 4 children resulted in practically normal curves. Significantly, in follow-up urinalyses, the reactions for melituria persisted in but a few cases.

When the urine of a sick child with acidosis exhibits both ketone bodies and alimentary melituria, the physician may suspect and hint at the possibility of diabetes to the parents.⁷ Needless to say, the mere mention of such an idea would excite great anxiety. Inasmuch as the great majority of episodes of glycosuria combined with ketonuria in acute illness during childhood are non-diabetic and of no permanent significance, the doctor should not voice his suspicion of mild or beginning diabetes until it becomes confirmed either by events of the next few days or by diagnostic studies made after the subsidence of the acute symptoms.

Renal Glycosuria. This diagnosis is made when there exists a harmless, chronic, non-progressive excretion of glucose with no symptoms of diabetes and with no hyperglycemia during fasting or after a meal. The quantity of sugar excreted may either fluctuate with variations in carbohydrate intake or be largely independent of the diet. The glucose tolerance curve is normal, as is the fat metabolism. There are no symptoms, and treatment is not needed. The injection of insulin with the subsequent reduction of blood sugar does not eliminate the glycosuria. The typical picture probably never changes to that of diabetes mellitus, but patients must be watched for some years before the differentiation can be established beyond doubt. Similar disturbances are often found in relatives of the patient. Marble^{100a} suggested that the respiratory quotient before and after a carbohydrate meal could be applied to prove the ability of the patient to store and utilize carbohydrate in a normal fashion, though the failure of mild diabetic patients to show such impairment under certain conditions¹²⁵ blocks the use of this determination as a criterion for differentiating mild diabetes from non-diabetic glycosuria. Subjects have been followed for as long as 20 years^{100b} without ever demonstrating any signs of diabetes or other disease attributable to the glycosuria.

John⁸⁰ objected to the adjective "renal" because "all glycosurias are renal in origin, depending upon the renal threshold as well as the glycemie level." The term normoglycemic glycosuria utilized by Powelson and Wilder¹²² is more logical, but as with so many other ill-fitted names in medical terminology, "renal glycosuria" is sustained by too great a weight of tradition to be easily displaced. According to Marble, who reflected Joslin's^{100b} views, the designation of renal glycosuria should not apply when the excretion of sugar is inconstant or intermittent, or if the morning fasting specimen contains no sugar. Fischer⁶¹ disagreed, stating that the question as to whether the glycosuria is continuous or intermittent depends solely on the threshold level of a particular patient. Fischer described 2 children who conformed to all the accepted criteria for renal diabetes save that in one the threshold for excretion was approximately 135 mg., and in the other, somewhere between 90 and 135 mg. Both were studied for a sufficient length of time to establish the non-diabetic nature of their disorder.

The hereditary character of renal glycosuria has been commented

on by all recent writers; in fact, most affected children are detected in family surveys made after an adult member has been found with the complaint. For example, Brown and Poleshuck²⁶ discovered 4 cases in 3 generations of one family. The grandchild, aged 10, like the other members, exhibited no symptoms or signs of diabetes mellitus, though urine specimens examined over a year all contained glucose. Following 60 gm. of glucose, by mouth, his blood sugar curve remained nearly horizontal, rising from a fasting level of 93 mg. per 100 ml. to 111 mg. after 30 minutes, and dropping to the base level by 1 hour. The quantity of sugar found in the urine was in trace amounts (0.03 to 0.5 mg. per 100 ml.); the more adult members of the family excreted larger quantities. On the other hand, there are cases such as Skolc's¹³⁹ with a negative family tree. This patient interestingly was given 20 to 50 units of insulin daily for several weeks with no effect on the output of urinary sugar, even on the one occasion when he approached insulin shock. The concentration of sugar in the urine in 7 of 933 children with renal glycosuria ranged from less than 0.3% to 5%.¹⁵⁹

Whether the glycosuria is present at birth or begins later on, has not been fully settled. The youngest known case was the month-old patient of Landabure.⁸⁴ There is some sex linkage: males are affected more frequently than females. The escape of sugar seems to persist continuously for the rest of life.

In adults, symptoms consequent to hypoglycemia were described by MacPherson.⁹⁸ These were minor degrees of faintness and weakness ascribed to a low fasting blood sugar level, and similar but more severe attacks attributed to relative hyperinsulinism following rapid loss of sugar in the urine. No reports of children having such episodes have been encountered.

Lead Poisoning. In studies carried out on a child having lead poisoning with glycosuria by Goettsch and Mason,⁷¹ the height of the blood sugar was consistently normal or lower than normal, and the urinary concentration of sugar remained relatively constant irrespective of the diet. The glycosuria persisted for 5 weeks, the concentration of urinary sugar diminishing as convalescence progressed. The authors suggested that the condition in lead poisoning may be classified as renal glycosuria secondary to intoxication of the kidney, and supported the suggestion by a survey of 8 cases of lead poisoning with glycosuria in children. In 5 cases the blood sugar values were normal; in 3 others in which dextrose tolerance curves were obtained the curves were not of the diabetic type. Glycosuria did not seem to alter the prognosis of the lead poisoning in these patients.

Intermittent Glycosuria. A puzzling phenomenon is the metabolic state in which glycosuria recurs intermittently for a time and then ceases altogether. Bayer and Davis¹⁵ described 9 such boys, aged 2 to 10.3 years, who because of recurrent glycosuria, were at first suspected of having early diabetes mellitus. However, their dextrose tolerance tests were normal at that time and there were no evidences of diabetes on reexamination 2 to 11 years later. The diagnoses made at the time of recheck were: normal, 6; unclassified glycosuria, 2; hyperglycemia after ingestion of glucose, 1. The rarity of this type of case is evidenced by the fact that collection of these 9 took 15 years, during which period some 50 children passed through the pediatric ward at the Stanford Univ. School of Medicine for study for possible diabetes mellitus. Bayer and Davis commented that, though the ultimate diagnoses of these glycosuria cases cannot be

foretold, it is unlikely that more than 1 or 2 would ultimately develop diabetes.

Diabetes Mellitus. The relationship between glycosuria and diabetes mellitus needs no discussion here. But one should remember that childhood diabetes may commence insidiously, that diabetic glycosuria at its beginning can be inconstant and intermittent. Mid-morning or mid-afternoon specimens may contain some sugar, perhaps but trace amounts, whereas those on rising in the morning may be entirely negative; hence it is wise to study thoroughly any child who exhibits glycosuria, even if positive specimens alternate with negative ones. A sugar tolerance curve after feeding carbohydrate for a few days is mandatory whenever there is the least uncertainty over the cause of the glycosuria. Non-elevated fasting specimens alone cannot be depended upon to exclude diabetes, since children with mild diabetes often may have normal or high normal levels when not taking food.

Transitory diabetes mellitus is a rarity, described but a few times. Söderling's^{142b} questionnaire, sent in 1935 to pediatric clinics all over the world, asked, among other questions, for information regarding completely subsided cases of diabetes in childhood, since the onset of insulin therapy. Only 2 spontaneously cured cases were submitted, 1 from Birmingham, England, and 1 from Toronto, Canada. Söderling^{142a} himself described a 5 year old child who recovered from a transitory attack of acute diabetic coma in association with pneumonia.

Fykov⁶⁶ reported a 2 year old boy with pneumonia, whose rapid breathing persisted after the temperature fell to normal. The urine at first contained acetone solely; sugar did not appear until 4 days later. The blood sugar rose to 312 mg. per 100 ml. A course of insulin treatment cured the patient's symptoms, though 4 months later the sugar tolerance curve was still abnormal, with a reading of 148 mg. 3 hours after glucose. Several other members of the family were found with abnormal blood sugar curves. Fykov suggested that this child with transitory diabetes would probably display permanent diabetes later in life, and advised a diet low in carbohydrates as a precautionary measure.

Essential Pentosuria. This has been defined as a "hereditary abnormality of metabolism characterized by continuous excretion of small amounts of pentose in the urine, unaffected by alterations in the diet" (Edelman and Reiner⁴⁹). These authors state that more than 170 cases have been reported, and refer to Blatherwick's estimate of an incidence of approximately 1:50,000 in the general population. The pentose excreted seems to be consistently xylulose. Under ordinary circumstances the daily output of pentose does not fluctuate either after changes in the carbohydrate or protein content of the diet or after periods of violent exercise followed by prolonged rest in bed, but does increase after feeding of its precursor *d*-glucuronic acid. On the grounds that identification was inadequate according to modern standards, Edelman and Reiner question seriously the reports from the first decade of this century that pentosuria occurs frequently in persons with severe diabetes. Many of the more contemporary workers, Marble,^{100b} for example, have searched for pentose in the urine of large numbers of diabetes patients with scant success.

The disorder appears to be a harmless metabolic phenomenon which is congenital and persists unchanged throughout life. Many patients have been Jewish. No special pathogenetic significance can be attached to cases which may be identified during infancy or childhood, as compared with others not discovered till later in life.

Fischer and Reiner⁶² conducted metabolic studies on 4 children aged 2 to 10 years having pentosuria. The non-fermentable reducing substances of their blood were not increased, and dextrose tolerance and blood pentose curves following ingestion of test amounts of these sugars were normal. There were no essential differences between the absorption and the excretion of pentoses in normal controls and in pentosuric children. Sunderman^{147b} found, on tracing the family of an 8 year old girl with the condition, that 2 of her 3 brothers and probably the mother were also affected. When Enklewitz and Lasker^{54a} fed 5 gm. of xylulose isolated from his own urine to a man with pentosuria, the rise which resulted was only 0.5 gm. more than the usual daily excretion. Thus the origin of the xylulose which appears in the urine of pentosuria remains unknown.

"Patients with essential pentosuria require no treatment except for the reassurance that they do not have diabetes mellitus."^{54b} This is well illustrated in the cases reported by Enklewitz and Lasker. A pair of twins, brother and sister, were studied for diabetes when 11 years old because of the daily excretion of 1.5 to 3 gm. of sugar in the urine. Seventeen years later they were still asymptomatic; the urine sugar, still persisting, was identified as xylulose.

Fructosuria. Fructosuria, known also as levulosuria, has been recently reviewed by Sachs, Sternfeld and Kraus,¹³⁴ who listed some 55 cases described since 1876 and added 2 others, children, personally observed. They commented that in 16 of the cases the data obtained was inadequate to fully establish the diagnosis. As regards age, 15 of the entire group were below 17 years of age when first studied, and 5 were younger than 7 years. The condition is clearly constitutional, and can be presumed to continue uninterruptedly from infancy throughout adult life.

In essential fructosuria, according to Silver and Reiner,¹³⁸ the sugar is always present in the urine except when the patient is given a fructose-free diet. The identity of the sugar can be established by its levorotary properties, the positive Seliwanoff test when the urine is acid, complete destruction by yeast fermentation, demonstration of a methylphenyl fructosazone, and normal dextrose tolerance curve. The sugar content should be the same when measured by optical rotation and by yeast fermentation.

Sachs, Sternfeld and Kraus¹³⁴ suggested that in these cases the mechanism for the fructosuria lies in the failure of ingested fructose to be broken down to lactic acid. In essential fructosuria, the respiratory quotient changes but slightly from the fasting value after the ingestion of fructose, and the level of lactic acid in the blood does not increase. In normal subjects, on the other hand, as shown by Deuel,⁴⁰ Bachmann and Haldi,¹¹ and Rynbergen, *et al.*,¹³³ the ingestion of fructose results in an increase in the respiratory quotient to unity or above, the rise occurring more promptly and the quotient rising higher than when dextrose is given. This phenomenon seems to be related to the normal tendency for fructose to induce a greater accumulation of lactic acid in the blood than does dextrose. Hence Sachs *et al.* propose that, when a normal person takes fruit or cane sugar or honey, some 80 % of the ingested fructose becomes converted to glycogen while the remainder breaks down to lactic acid; whereas when an individual with essential fructosuria ingests these foods, some 10 to 20 % of the ingested fructose fails to become metabolized, and instead is excreted intact in the urine. "The abnormality may lie in the failure or lack of some specific enzymatic action, the site of which has not yet been determined but which may be in the intestine, the blood or the liver."

Debré *et al.*³⁹ described a 6 months old infant with furunculosis, who for 10 days exhibited a pronounced fructosuria while being fed sweetened condensed milk rich in sucrose. The fructosuria disappeared when the diet was changed to one low in sucrose. Four months later the fructosuria could not be reestablished by liberal feeding of fructose and sucrose. Evidently during the period of infection this infant's liver was not functioning adequately; it failed to convert into glycogen all the fructose brought to it from the site of sucrose splitting in the intestine.

Galactosuria. A few cases with malnutrition and galactosuria have been reported, the one of Mason and Turner¹⁰³ being the most intensively studied. This infant, followed from 6 months to 3 years of age, did not gain normally so long as the diet contained milk. He showed marked enlargement of the liver, slight enlargement of the spleen and superficial lymph nodes, positive reaction to the van den Bergh test, secondary anemia, osteoporosis of the bones and protein and galactose in the urine. Removal of milk from the diet resulted in the disappearance of sugar and protein from the urine, decrease in the size of the liver and spleen, disappearance of the other findings and a rapid gain in weight. The curves for blood sugar after the ingestion of dextrose and levulose were within normal limits, but those for lactose and galactose were abnormal as a consequence of pathologic increases in the level of blood galactose. Mason and Turner suggested that the primary trouble was a lesion or functional disturbance in an otherwise normal liver, impairing the ability of this organ to convert galactose into glycogen, and that the derangement in the other tissues was the result of relative starvation due to the continuously low level of blood dextrose.

In addition to the above case, in recent years Fanconi^{58b,c} described a 9 year old boy with familial neurofibromatosis, zonular cataract and galactosuria, and Lescovar⁹⁰ a 4 week old galactosuric infant who expired at 4 weeks of sepsis and cholangitic cirrhosis of the liver. It is likely, however, that the incidence of the disorder is higher than indicated by the paucity of published reports. Every child suspected of having von Gierke's "glycogen disease" with recurrent melituria (*vide infra*) should be studied carefully for galactosuria.

Mason and Turner's patient, when given 25 gm. of galactose in a 7-hour tolerance test, excreted only 6.64 gm. during the period, evidently storing or catabolizing the difference. Fanconi's patient, on the other hand, excreted 1 gm. in the urine after being given 2 gm.; after 6 gm. he excreted 5.2 gm.; the larger dose caused a rise of blood sugar to 466 mg. per 100 ml. and symptoms of apathy and weakness. Thus the metabolism of galactose in such cases may be imperfect, but is not wholly inadequate.

No cases of urinary elimination of the disaccharide lactose, such as occurs at times in women during pregnancy or later during lactation, were found reported in the 10-year period covered by this Review.

Sucrosuria. A 7 months old infant with saccharosuria (sucrosuria) was reported by Reiner and Weiner.¹²⁸ The saccharosuria occurred both when saccharose itself was given in excess and when it was fed in lesser amounts along with other sugars, which appear to compete for prior digestion and absorption. Thus the saccharosuria appeared to be alimentary in origin. Reiner and Weiner theorized that, in the presence of infection, either enteric or parenteral, increased intestinal permeability may result in absorption of disaccharides. In their child, the disturbance was demonstrated at the ages of 7 and 18 months when certain combinations of carbohydrates were given. Elmer, Krasowska and Ptaszek⁵² describe

an adult case, and state that there are only 2 other cases in the literature (both adults) besides theirs and that of Reiner and Weiner. They discuss the physiologic sucrosuria which follows the taking of large amounts of cane sugar, commenting that after 150 to 250 gm. of cane sugar are taken by mouth the urinary excretion will not exceed 1% of this amount, the remainder being hydrolyzed in the intestine. Masserman¹⁰⁴ has shown that 90 to 100% of intravenous sucrose will be excreted.

It should be remembered that disaccharides will not react with Benedict's solution unless the urine is first acidified and boiled to hydrolyze the sugar into its component hexoses.

Glycogen Storage Disease (von Gierke). The clinical and pathologic data on all cases reported as glycogen storage diseases were collected and analyzed critically by Mason and Andersen.¹⁰² They succeeded in classifying the cases into 5 separate types, each with a different fundamental defect. Of the 34 cases of the hepatomegalic type in their collection, it has been pointed out⁹⁹ that urinary sugar was present in only 2 of the 23 cases in which tests for sugar in the urine were reported. Manter and Bowman⁹⁹ described another instance, a 14 month old boy, in whom glycosuria was intermittently present. In this patient the glycogen of the liver apparently was not abnormal, but the glycogen metabolism was deranged as shown by ketonuria, deficient storage of ingested dextrose, inability to mobilize dextrose from large amounts of glycogen in the liver when epinephrine was injected, and failure of hepatic glycogenolysis after death. Manter and Bowman explained the glycosuria in terms of a low renal threshold, while suggesting that it may have been related in some way to the glycogen found in small amounts in the epithelium of the renal collecting tubules after death.

The Fanconi Syndrome. A number of cases of refractory rickets have been reported in which non-diabetic glycosuria was a prominent associated feature. This syndrome, first separated from the larger group of so-called renal rickets by de Toni⁴¹ in 1933 and Fanconi⁵⁸ in 1936, is characterized in general by severe intractable hypophosphatemic rickets, renal glycosuria, polyuria, and acidosis with extreme reduction of the serum bicarbonate. It appears to be congenital in origin. In the case of McCune, Mason and Clarke¹⁰⁶ the protein nitrogen and urea of the blood were normal, but the urine contained large amounts of protein, ammonia, lactic acid, betahydroxybutyric acid and amino acids. A balance study revealed excessive excretion of phosphorus and calcium by the kidneys. The metabolism of sodium, chlorine and magnesium appeared unaffected. Treatment with 5000 U.S.P. units of vitamin D daily for several weeks caused no evident improvement.

On reviewing the reports on record, McCune *et al.*¹⁰⁶ found 28 seemingly related cases in infants and children and 2 others in adults in whom rickets was replaced by osteoporosis. They concluded that the Fanconi syndrome, with its combination of rickets, hypophosphatemia and renal glycosuria is not a sharply definable clinical entity, but without perceptible demarcation merges with classic hyperphosphatemic renal rickets on the one hand, and with the poorly understood process known as cystine rickets on the other. They hypothesized that the fundamental defect is a diminished ability of the renal tubular epithelium to resorb dextrose, amino acids and phosphate from the glomerular filtrate. To neutralize the undue amounts of organic acids, large quantities of ammonia and mineral cations are excreted, with consequent depletion of the total base of the body fluids. Recurrent hypoglycemia was thought to be responsible for the excretion

of betahydroxybutyric acid, and the presence of lactic acid was ascribed hypothetically to a dyscrasia of either the renal tubules or the liver.

According to McCune *et al.*, the concentration of reducing substances in the urine can vary between a trace and 4 or 5%. The excretion of sugar is characteristically continuous, at least in patients with the more severe forms of the syndrome; though it may be intermittent and disappear for considerable periods of time. On investigation, the reducing substance is usually found to be dextrose. However, Lignac's⁹⁴ patient first excreted a pentose and later a substance, the osazone of which melted at the temperature of lactosazone; Gittleman and Pincus⁷⁰ reported dextrose and fructose in nearly equal concentrations; van Creveld^{153a} ascribed part of the reducing capacity of his patient's urine to glycuronic acid with dextrose also present in concentrations of 1 to 2%. The fasting blood sugar level ranged from 48 mg. to 160 mg. per 100 ml. The glycosuria varied in intensity with changing levels of blood sugar but was characteristically present at all times, even when the blood sugar was low. During the oral administration of dextrose for test purposes, Debré's³⁸ patient became restless and pallid and then lapsed into fatal coma, and 2 of Fanconi's⁵⁸ patients were rendered extremely uncomfortable but survived.

In most cases the volume of the urine was moderately increased. Despite the large volume of urine, McCune *et al.*¹⁰⁶ noted that the specific gravity was frequently high, due to the presence of sugar, protein and other solutes. Proteinuria of moderate degree was a consistent phenomenon; casts, leukocytes and epithelial cells were often present. Microscopic hematuria was reported occasionally. Despite the demands made by acidosis, the pH of the urine was frequently 6.5 or higher, though McCune's case occasionally assumed values as low as 4.8. High urinary concentration of ammonia, and especially large quantities of phosphates and organic acids were always encountered when searched for.

4. **Sulfonamides.** The pathologic changes in the urinary tract resulting from administration of sulfonamide drugs was thoroughly summarized in a review published in this Journal several years ago by Peterson and Finland;¹¹⁹ not much new has been learned since then. Direct renal damage with sulfanilamide and sulfadiazine is quite uncommon, whereas sulfapyridine and sulfathiazole exert the largest share of their toxic effects upon the kidney. The lesions in the urinary tract are produced mainly by crystalline sulfonamides which precipitate out, mixed with blood and amorphous matter, anywhere along the tract from renal tubules to bladder. Hemorrhages follow, the urine flow becomes obstructed, the passages dilate above the obstruction, and the kidneys grow large and edematous. Or there may be direct necrotoxic changes, with glomerular reactions and epithelial degeneration of the tubules. In some instances, both kinds of injury have been recognized in the same kidney.

Crystalluria and Hematuria. The specific solubility of the various sulfonamide compounds and their acetylated derivatives determines in large measure the frequency and the quantity of the crystals which appear in the urine. *Sulfadiazine* and *acetyl sulfadiazine*, which are the most soluble, are the least likely to give rise to urinary tract disturbances. *Acetyl sulfathiazole* is much less soluble in urine than is the *free* form, and both substances are slightly more soluble in alkaline than in acid urine. This difference did not seem of sufficient magnitude to Peterson and Finland to warrant alkalization of the urine as a precaution against renal complications during sulfathiazole therapy, whereas Sunderman and Pepper¹⁴⁸ did make that recommendation. With *sulfanilamide*^{35,59,101} the

acetylated form is one-third as soluble as is the free drug under similar conditions. *Sulfadiazine*,^{68,130} *sulfamerazine*⁶⁹ and *sulfamethazine*⁶⁹ and their N₄ acetyl derivatives increase markedly in solubility with a rise in pH from 5 to 8; *sulfapyridine* and *acetyl sulfapyridine* do not.¹¹⁹ All observers agree that when pH conditions favor solubility, or when there is a good diuresis, the crystalluria and hematuria are usually inhibited, whereas with unfavorable urinary pH and scanty urine the likelihood of such difficulties becomes enhanced.

Urinary crystals and renal stones in patients taking sulfadiazine are about 93% acetyl sulfadiazine, and the solubility of the acetyl portion of these urinary crystals is similar to that of pure acetyl sulfadiazine. Clinical studies suggested by these solubility findings¹⁴⁸ revealed the incidence of crystalluria to be 27% in 172 acid urines and but 1.4% in 147 neutral or alkaline urines. It follows from these observations that patients receiving sulfadiazine be given alkali along with it, in order that the urine be kept neutral or alkaline and the precipitation of sulfadiazine compounds in the urinary tract be prevented. This procedure seems especially necessary when large doses of this drug are being given over a protracted period of time. The dosage of alkali can be regulated by watching the pH of the urine; enough should be administered to keep the pH at 7.5 or higher. Nitrazine paper is helpful for this purpose; with children sick at home the parents can be instructed as to its use. When small doses of sulfadiazine are given for but a few days the precaution is less essential.

The crystals observed in specimens often form and settle out as the urine stands in the bottle at room temperature. From the standpoint of urinalysis, therefore, the discovery of crystals does not necessarily hint at internal crystallization unless the urine is warm and freshly voided, or unless red cells are also present. If they appear under these circumstances, one should be alert for crystal deposit and calculi formation within the urinary tract. Precautionary fluids should be forced and alkalis given to assure the pH of optimal solubility in the urine. The drug should be discontinued and urologic procedures resorted to if indicated.⁷⁹

Hematuria is the danger signal. Children receiving any of these drugs in large quantities or for more than a few days should have a microscopic urinalysis every 2nd day, in order to detect renal irritation in its beginning stages. In adults, according to Smith,¹⁴⁰ the frequency of sulfonamide hematuria is as follows: sulfapyridine, 2 to 3%; sulfathiazole, 2 to 3%; sulfadiazine, 0.5 to 1%. Oliguria, too, has occurred in a small percentage of cases receiving sulfapyridine, sulfathiazole or sulfadiazine. Of 53 children with assorted infections treated with sulfathiazole by Dowrie and Abramson,⁴⁵ only 1 showed hematuria in daily urinalysis; 2 of 54 children receiving sulfadiazine exhibited hematuria. The experience of Winters and Janney¹⁶¹ is in contrast with the above low figures. Of 90 children hospitalized and given sulfadiazine for infectious diseases of wide diversity, 12 had erythrocytes and 18 had both sulfadiazine crystals and erythrocytes in the urine. These toxic effects cleared when the dosage was lowered.

The drug sulfamerazine is too new for the publication of reports on its toxicity in the early years of life, but to judge from personal experience the incidence of urinary findings would seem to be at least as common as with sulfadiazine. On comparing 428 adult patients treated with sulfamerazine against 900 controls treated with sulfadiazine, Dowling *et al.*⁴⁴ found the incidence of renal calculi higher in the sulfamerazine group when identical doses of each drug were given.

The concentrations of the various sulfonamides in freshly passed urine are higher than can be secured by dissolving the same substances in water or urine *in vitro*. It has been suggested that these drugs may be excreted as highly soluble glucuronates or related substances. Lehr and Antopol⁸⁸ proposed that protective colloids in the urine serve to inhibit the sulfonamide precipitation. They found that the comparatively insoluble acetyl derivatives which form in the body from sulfapyridine, sulfathiazole and sulfadiazine, if analyzed as urinary crystals, showed a markedly depressed melting point; on recrystallization the solubilities approached or reached those of the pure synthetic compounds.

The Wood Fiber or "Lignin" Test. A new "easy, rapid and reliable" test for the presence of sulfonamides in urine has come into wide use within the past 2 years. Originally proposed by Hallay,⁷⁵ favorable reports soon followed by Bogen,²³ Kawaichi⁸³ and Hubata,⁷⁸ and the Reviewer can sponsor its reliability from extensive personal experience. The essence of the test is the production of a yellow or orange color when any of the sulfonamides, which all contain the aniline group, react with wood fiber in the presence of acids. To perform the test, one acidifies with a few drops of 4% HCl a fragment of newsprint paper, paper toweling (not rag paper), sawdust, or tongue depressor, adds a few drops of urine, and watches for the appearance of the distinctive color. Kawaichi states that the color is yellow when the concentration of the drug in urine is 100 mg. or less; orange when above 100 mg.; and that there is danger of sulfonamide concretions when the concentration is above 100 mg.

In our experience the color change reaches its visible maximum at about 70 to 80 mg. free (unacetylated) sulfonamide. It is easy to establish that this color reaction is produced only by the free form of the sulfonamides, with the acetyl derivatives playing no part.

The physician prescribing sulfonamides will feel diminished anxiety regarding danger of calculus formation if the urines of his patients are kept sufficiently dilute to yield a yellow rather than orange color with the wood fiber test, and are also at the pH of optimal solubility (above pH 7 with sulfadiazine) when checked with nitrazine or litmus paper.

5. Pigments. The color of urine normally varies from pale to dark amber, the shade depending chiefly upon the content of urochrome. Drabkin⁴⁶ found the output of this pigment to be a constant quantity from day to day in state of health, but augmented by fasting, fever, hyperthyroidism, and all factors which stimulate endogenous metabolism. Normal urine may also contain trace amounts of hematoporphyrin, uroerythrin and urobilin.

Under abnormal circumstances, other pigments may escape from the body fluids into the urine. Some of these, such as anthocyanin, result from diet or medication; some, such as urobilin, hemoglobin and its derivatives, and melanin, indicate systemic disease; and others, such as the porphyrins and homogentisic acid, are manifestations of congenital errors of metabolism. Selected for consideration here are comments from recent noteworthy papers.

Anthocyanin. The red pigmentation of the urine which sometimes follows the eating of red beets is due to anthocyanin, the principal pigment of the beet, and may vary from light to dark red. Matheson¹⁰⁵ and Poole¹²⁰ have each described cases, and most pediatricians are familiar with its occurrence. The pigment can be quickly differentiated from hemoglobin by adding alkali, such as potassium hydroxide or sodium hydroxide solution, to the urine. The color becomes deep yellow when alkalinized,

and will revert to the original red when acidified once more. No one knows why anthocyaninuria is infrequent when beets are so common in the diet of children.

Urobilin. According to Josephs,^{81,82} the normal child excretes the bulk of his urobilin in the stools, the urine urobilin constituting but 5% of the total daily excretion. In infancy and early childhood the total 24-hour urinary excretion of urobilin can be expected to be but 1 or 2 mg.; in pre-adolescence and puberty, 4 to 5 mg. These small amounts escape detection by the usual tests. When there is anemia of hemolytic origin, however, the total excretion of urobilin increases strikingly, often reaching 20 to 30 times the normal. The urine then becomes positive for urobilin, though the ratio between stool and urine urobilin remains about the same as in normals. Only in cases of extensive liver damage did Josephs find the proportion of urinary to fecal urobilin to be elevated, attaining ratios of 10 to 20% or higher.

The term "urobilin" covers a number of substances of unknown composition giving fluorescence in alcoholic zinc acetate. On first appearing in the urine these substances exist in the chromogenic or urobilinogen state, but become oxidized on exposure to air, and after a few hours change to urobilin itself. From the standpoint of the laboratory technician, the standard test for urobilinogen—that of Ehrlich—is easier to perform than that for urobilin. Specimens to be tested for urobilinogen should reach the laboratory fresh, within the first few hours of passage, before this change occurs. Because relatively small amounts reach the urine, quantitative tests for urobilinogen meet no special clinical need; when information regarding total urobilin excretion is desired, the stool analysis yields adequate information. In searching for the presence of urobilin in a patient with possible undue hemolysis, it is wise to repeat the test daily for several days, since excretion of excess urobilin may be erratic and irregular.

Homogentisic Acid. Alcaptonuria is an outward manifestation of a very rare congenital anomaly of protein metabolism in which homogentisic acid is excreted in the urine. This substance, colorless itself, darkens on standing, due to oxidation. It reduces Benedict's solution, but fermentation tests for sugar are negative. In enuretics the bed linens often turn dark as the urine undergoes ammoniacal decomposition. Abbott¹ described the condition as it occurred in 2 Negro siblings, the first instances to be reported in the American Negro. Addition of 10% sodium hydroxide solution to the clear urine resulted in a brownish black ring at the surface which gradually penetrated downward, ferric chloride solution caused a transitory blue color with each drop, and reduction of silver lactate and of ammoniacal silver nitrate proceeded rapidly at room temperature. The concentration of homogentisic acid was found to be 4.4 to 5 gm. per liter, and the homogentisic acid to nitrogen (H:N) ratio ranged from 45.1:100 to 53.5:100. It was possible to precipitate out the lead salt of homogentisic acid from the urine of both children.

Of the numerous other cases recently reported, that of Lelkes⁸⁹ is exceptional in that the mother of his 3 months old affected infant had also had alcaptonuria as a child, and this had ceased spontaneously when she became 12 years of age.

Porphyria. Porphyria, a more descriptive term than porphyrinuria, is a constitutional state marked by the excretion of porphyrins either in greater than physiologic amounts or in kinds not normally demonstrable. In the congenital variety, according to Dobriner and Rhoads,⁴³ the classical

manifestations consist of excretion of large amounts of porphyrin, discoloration of the teeth and bones by impregnated uroporphyrin, and sensitivity of the skin to light in the spring and summer. Blistering of the exposed areas of the face and extremities is observed, and the lesions heal with scar formation, followed in many cases by deformity of the affected part. Turner and Obermayer¹⁵³ were able to find but 86 cases on record up to 1936. Only one-half of these had had symptoms beginning prior to puberty.

The urine may vary from pale pink to red to almost black, though usually Burgundy red. Often the urine when passed is a normal yellow, but darkens later when exposed to light, sunlight being most effective. For details concerning this unusual condition the reader is referred to Turner and Obermayer,¹⁵³ Dobrinier and Rhoads,⁴³ and Watson.¹⁵⁶ The pathogenesis of this disturbance is not known. The pigments in the urine are chiefly coproporphyrin Type 1 and uroporphyrin Type 1, as well as some brown urofuscins. If present in quantity, they can usually be identified by study of the absorption spectra. Guild⁷⁴ was able to prevent active symptoms in one patient by liver extracts in large doses.

6. Findings in Newborn and Premature Infants. The past decade has made but few contributions to general information concerning the character of the urine in the neonatal period. The most extensive report on newborns is by Tausch,¹⁵¹ who reviewed much of the earlier literature and described his own observations in detail. Tausch catheterized some 4000 newborn infants promptly after delivery and was able to secure urine specimens in 2837, the remainder having presumably voided while passing through the birth canal. In quantity the urine varied up to 44 ml., averaging 5.7 ml. There was no sex difference and no relationship between duration of labor and quantity. The color varied from colorless to deep yellow, 27% being free from color. The specific gravity had a mean of 1.0097 and a range of 1.004 to 1.019. Specific gravity showed a definite relation to body weight, the means for increasing weight groups progressing from 1.0072 in those under 2500 gm. up to 1.0112 for those between 3500 and 4000 gm. In reaction, 1794 were acid, 164 alkaline, and 879 neutral. A review of the literature was given to show that proteinuria is common in the first day of life. The author's figures showed 403, or 14.21% of the 2837, positive for protein, 215 (7.59%) markedly so. Tausch failed to find any significant correlation between proteinuria and kidney disease in the mother, or to duration of passage through the birth canal. Infants delivered by Cesarean section showed approximately the same incidence of proteinuria as those born in the usual fashion. In only one instance was the urine grossly bloody; 32 had microscopic red cells, 59 had leukocytes and 8 had casts. Bile was not present in any case. Although the literature reviewed showed that reducing substances occur occasionally, the author failed to find any specimens containing sugar in his series, even in the operative and difficult labor cases.

The above observations on the composition of what may be termed urine accumulated *in utero* can be compared with those of Faerber⁵⁷ on postnatal urine. On comparing clinical appearances with weight curves, fluid intake, body temperature and protein content of the blood in 30 newborns from 1 to 10 days old, Faerber found that albuminuria and excretion of casts and leukocytes ran parallel with dehydration. These positive findings disappeared after the fluid intake had become about 10% of the body weight.

Allyn and Allyn⁶ have reported on the urinary findings in the newborn

given ammoniated mercury rubs for the prevention of impetigo. In a total group of 220 infants, tested on the 5th and usually again on the 7th day of life, a positive sugar reaction was found 4 times. In addition, 18 specimens showed "trace" amounts of reducing substances. Of these, 132 babies received inunctions of $3\frac{3}{4}$ ammoniated mercury, and 88 served as controls. Of the group receiving the rubs, 18% had protein, 63% had leukocytes, and 5% a few red cells. Of the controls, only 4% had protein, 28% had leukocytes and 1% had a few red cells. These differences were interpreted as indicative of mild renal irritation from the ointment. The data are informative also in that the findings in the controls are representative for normal American newborns.

That the early fetal kidney can and does function now is well established, though the evidence rests chiefly upon animal experimentation. The literature on this topic has been well reviewed by Needham.¹¹⁵ Cameron and Chambers³¹ have been able to furnish the first direct evidence that human embryonic proximal tubules of themselves are able to function. They studied a living human fetus immediately after delivery by Cæsarian section, of age estimated at $3\frac{1}{2}$ months. They found that the cut ends of segments of the tubules of the embryo kidney healed over in tissue culture, and that certain dyes, if present in the surrounding medium, passed into and accumulated in the lumina of the proximal tubules to a conspicuously higher concentration than that of the dyes in the medium. The experiments with phenol red showed that the proximal tubular fluid of the human metanephros has a pH of approximately 7.

7. *Miscellaneous. Acetone.* Ketosis with acetonuria is more common in children than in adults, and carbohydrate impoverishment plays a rôle in its production.^{77,158} The modern conception of the physiologic mechanisms underlying the development of ketosis have been succinctly stated by Mirsky and Nelson¹¹¹ in their recent study on ketosis in children: "It has been demonstrated that the liver is the main site of the formation of ketone bodies; that any phenomenon which induces a depletion of the glycogen reserve in the liver will produce ketonemia; that the administration of adequate amounts of exogenous sugars can inhibit the formation of ketone bodies in diabetic and in non-diabetic organisms, even in the absence of insulin in the former; that the muscles of diabetic and of normal animals utilize ketone bodies with equal avidity; that there is a maximal rate at which ketone bodies are utilized by the muscles, and that excessive ketonemia will occur only when the rate of production exceeds that of utilization; that carbohydrate metabolism does not affect the rate at which ketone bodies are burned in the muscles, and that so long as the organism can maintain an adequate store or reserve of glycogen in the liver the rate of fat metabolism, and therefore the rate of formation of ketone bodies, cannot become sufficiently increased to cause an excessive ketonemia. Accordingly, it may now be stated that fats do not 'burn in the flames of carbohydrate' but 'the flames of carbohydrate inhibit those of fat'."

Thus, any phenomenon such as high body temperature which increases the metabolic need of the muscles for carbohydrate or which decreases the availability of carbohydrate for storage in the liver (*e. g.*, vomiting) will favor the development of ketonemia. It is wise, therefore, to give frequent meals and feed sugar-containing substances, at night as well as during the day, if necessary, whenever a child becomes ill with any infection or metabolic disturbance. This undue administration of carbohydrate will

counteract the heightened susceptibility to ketosis of the sick child and help to prevent the development of acidosis.

Experimentally, Mirsky and Nelson found that phlorhizin glycosuria with a loss of 15 to 20 gm. of sugar from the normal child, or of a lesser amount from the diabetic child, resulted in hypoglycemia and ketonemia secondary to glycogen impoverishment of the liver. The younger the child, the smaller the reserve of glycogen in the liver, relatively speaking; this explains the greater susceptibility of younger children to ketonemia.

Amylase. That the amylase content of urine and blood becomes elevated during mumps is well established^{47,60,93,113}. High values may be found also in pancreatic diseases such as acute pancreatitis and obstruction of the common duct by stone, but such disorders enter pediatric differential diagnosis but rarely. The source of the excess of enzyme is presumably the affected glands—pancreas, parotids, etc. Urinary amylase may be present after the 2nd day of mumps, according to Dunlop,⁴⁷ who studied 60 cases. Since the titer in his patients was comparable with that of acute pancreatitis, he wondered whether pancreatitis occurred more frequently in mumps than is commonly supposed. He made it a rule to keep patients with mumps in isolation until the urinary amylase had returned to normal, which was often some days after parotid swelling had subsided. The determination of diastase in blood or urine can be helpful in distinguishing other localized infections of the neck, such as cervical adenopathy, from mumps.

Calcium. Excessive urinary calcium excretion can be detected by the simple test introduced by Barney and Sulkowitch¹³ in 1937. When acidified urine is shaken with an equal amount of buffered oxalate solution of stated strength, an immediate dense cloud of calcium oxalate indicates a high concentration of calcium, whereas the absence of any precipitate almost always rules out excessive parathyroid activity. At the time of the test the diet must be free from milk, cheese and acidifying agents, since these can cause temporary increases in calcium excretion.

Albright⁵ recommended the test for control of the dihydrotachysterol treatment of hyperparathyroidism. With patients on a high calcium diet the dose of dihydrotachysterol should be so regulated that the urine will not display a heavy cloud; in this way the serum calcium can be kept at a safe, slightly subnormal level.

The possible value of this test in detecting abnormal calcium metabolism in children was explored by Linder and Latsky⁹⁵ in a series of 114 children aged 9 to 15 years. They found no correlation between the mean serum calcium levels and the urinary reactions. A tendency was noted for the malnourished children with a serum calcium below 8.5 mg. per 100 ml. to give a negative test in specimens collected after breakfast. There were so many exceptions that they were forced to conclude that the Sulkowitch test for urinary calcium has only a very limited use in a nutrition survey. Linder and Latsky noted, as Barney and Sulkowitch, and Albright had done, that if several cups of water were given to children arriving with a "thick" test, the urine passed subsequently would be "clear." Reversely, the giving of milk caused "clear" urine to become "thick."

Obviously any test whose responses are so dependent upon the drinking of milk, which is a staple during the early years of life, and upon fluid intake, has scanty application to the field of pediatrics. Nevertheless it has proved helpful as a guide to therapy in hyperparathyroidism, both the primary variety and that associated with renal insufficiency.

Chlorides. Expressed as sodium chloride, the daily output of urine chlorides in the healthy child is about 3 to 10 gm., being roughly proportional to age. The excretion reflects the intake in the diet. Excessive perspiration, diarrhea, pneumonia, nephritis and some other disease states will cause a urinary decrease. With the usual attack of pneumonia the urinary chloride drops to exaggerated low levels just prior to the crisis, reaches the lowest level at the time of the crisis, and then 1 to 3 days later rises abruptly to supernormal levels for 24 to 48 hours followed by prompt return to normal.^{72,147,160} Antopol and Churg⁹ followed 17 patients with pneumococcus pneumonia treated with sulfapyridine. The urinary chlorides began to rise on the 6th to 14th day of illness, the 3rd to 7th day after initiation of sulfapyridine therapy. Thus the chloride rise took place from 2 to 6 days, in a majority 4 to 5 days, following the crisis. Of the 17 cases, 9 were children from 9 months to six years. In 5 patients with sulfathiazole-treated pneumonia, Oshlag and Eil¹¹⁷ noted similarly that clinical defervescence occurred several days ahead of the sudden reappearance of chloride in the urine.

Sherman and Corbin¹³⁷ using a simple qualitative test, described their experiences with the urines from approximately 300 children in 2 Chicago hospitals. Of these, 123 had greatly reduced or nearly absent urinary chlorides. In this latter group 82 (67%), had pneumonia and 19 (15%), had upper respiratory infections, leaving a miscellaneous collection of 22 (18%), with varied conditions; namely, 5 with prematurity, 4 prodromal measles, 2 peritonitis, 2 pneumonic and 1 influenzal meningitis, 2 nephritis, 2 eczema and 1 each of gastro-enteritis, sickle cell anemia, and acute appendicitis. They accounted for the decreased chlorides in the miscellaneous group on the basis of insufficient intake by the prematures and dehydration, edema, diarrhea or vomiting in most of the others.

Cystine. The metabolic fault in cystinuria appears to be an inability to oxidize the normal proportion of endogenous sulfur to sulfate, and to excrete it as such. Instead, unusually large quantities of cystine enter the urine, and tend, on standing, to settle out as characteristic flat hexagonal crystals. The level of cystine excretion in the cystinuric is fairly constant, but it can be raised by a high protein diet, independent of the sulfur content of the particular proteins eaten.¹⁰⁹ Brand, Harris and Bilon²⁵ have described a qualitative cyanide-nitroprusside test which makes possible quick screening of urine for cystine. If this reaction is positive, the more difficult Sullivan¹⁴⁶ naphthoquinone should be done to confirm the finding.

The familial incidence of cystinuria is now well established. Lewis⁹² encountered 4 frank cases and 14 likely ones in 11,000 urines of healthy young male and female college students. In adults, the condition is typically benign and usually not suspected, but occasionally such subjects develop symptoms from cysteine calculi. The urologists recognize that the danger of calculus formation is always present, and have found that an alkaline ash diet low in protein is helpful in preventing stones from forming. Andrews and Brooks⁸ state that there are no cases on record in which a cystinuric subject has ever formed a calculus of any other composition than practically pure cystine.

In children, cystinuria may provoke more violent disturbances than those above described. Cases have been reported by Abderhalden,² Lignac⁹⁴ (3 cases), Fanconi,⁵⁸ and Beumer and Wepler,¹⁹ of young children who died with symptoms of nutritional failure, and at postmortem had cystine crystals in many organs by both microscopic and chemical examination. These autopsy findings suggest that enzymatic inability to metab-

olize essential cystine was the mechanism behind their failure of normal growth and nutrition. Three of these 6 cases had proteinuria and renal glycosuria, attributed to malfunction of the infiltrated kidney.

Indican. Several studies on the excretion of this substance have been reported by Sharlit.¹³⁶ Indole, which is formed solely in the intestines from tryptophane, is detoxified by the liver through oxidation to indoxyl and conjugation with sulfuric acid to form potassium indoxyl sulfate, or indican. The excretion of large amounts of indican in the urine may be accepted as evidence of inordinate putrefaction of protein in the intestine. Sharlit^{136b} collected single chance specimens of urine from each of 35 infants between 2 months and 2 years of age, each of whom had an eruption—usually some form of eczema. The quantities ranged from faint trace to 87 mg. per liter—values which were probably in excess of normal amounts, though distinctly less than might be expected from protein putrefaction due to intestinal stasis of any marked degree. Sharlit^{136a} found also that newborns aged 3 to 19 days excrete appreciable amounts, though he made no attempt to correlate the quantities with the exact daily age, laxation rate or kind of milk being fed.

Phenylpyruvic Oligophrenia. This is a rare metabolic error, congenital and hereditary, characterized by mental deficiency, neurologic disturbances and phenylpyruvic acid in the urine. Dann, Marples, and Levine³⁷ subjected a 25 month old boy with this disease to extensive metabolic tests. They found his urinary content of this substance to vary from 0.45 to 1.03 gm. per 24 hours. Appreciable amounts of phenyllactic acid (0.20 to 0.55 gm.) and of phenylalanine (0.21 to 0.32 gm.) were also being excreted. On the basis of these and other experimental findings they concluded that the defect in this disease is an inability to properly metabolize phenylalanine. Ascorbic acid in large doses did not induce improvement. For accuracy in diagnosis, the authors recommend a urine examination for phenylpyruvic acid of every infant and child suspected of being mentally retarded. The test is easy to perform. If phenylpyruvic acid is present, acidified urine, when 5% ferric chloride solution is added, assumes a transient characteristic green color.

17-Keto Steroids. The urinary excretion of 17-keto steroids in children has been reported on by Talbot and associates.¹⁴⁹ The output of these substances was very low from birth to approximately 10 years, rising gradually with older children as they approached 18 years of age, with no significant difference between boys and girls. During the period from 8 to 18 years, the average output rose from less than 1 mg. to approximately 9 mg. per day. Because values approximating 0 mg. may be considered normal for children under 10 years of age, detection of abnormally low excretion in children under that age is not possible. However, children who have reached their 12th birthday should excrete at least 1 mg. of 17-keto steroids daily. A tendency toward moderate elevation in output of 17-keto steroids was observed in apparently "normal" children with physiologic sexual precocity and in abnormally overweight children whose development tended to be accelerated. Abnormally low values for excretion were obtained for children over 12 years old whose growth and development were retarded. The excretion of 17-keto steroids of patients with mongolism was not consistently abnormal.

Tyrosine and Phenylalanine. A spontaneous defect in the metabolism of tyrosine and phenylalanine was discovered by Levine, Marples and Gordon⁹¹ in premature infants being raised on cow's milk. Full-term infants on similar diets did not excrete these aromatic amino acids. Chrom-

ogens were encountered, while studying the urinary excretion of creatinine by prematures, which gave the Jaffe reaction but none of the other characteristic tests for creatinine. By careful analysis these substances were found to be *l*-p-hydroxyphenyllactic and p-hydroxyphenylpyruvic acids. When these amino acids were fed in pure form their urinary excretion became augmented. When the feeding mixture contained 5 gm. or more of cow's milk protein per kg. body weight per day, these abnormal substances were present in quantities of 300 to 500 mg. of tyrosine equivalent per kg. body weight per 24 hours. On the other hand, with breast milk, which contains much less protein, or with a cow's milk mixture of greatly reduced protein content, the daily excretion fell to below 10 mg. The authors were able to show that this behavior was brought out most fully when there was no vitamin C in the diet. Conversely, the administration of *l*-ascorbic acid completely eradicated the defect without necessarily raising the plasma ascorbic acid level. The administration of *d*-isoascorbic acid had a less definite partial effect. None of the other known vitamins produced any improvement. The reversibility of this metabolic aberration differentiates it from such hereditary anomalies as alkaptonuria and phenylpyruvic oligophrenia which are not correctible with vitamin C.

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GYNECOLOGY AND OBSTETRICS

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CANCER OF THE CERVIX

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THE problem of cancer is far from solved, but each year one or two bits of information are unearthed which may be small pieces in the gigantic

jig-saw puzzle. While the present status of the situation is not too encouraging, there can be no doubt that, on the whole, our knowledge of the subject and the results of treatment are improving. Until we know the cause of cancer, treatment cannot be fully efficient, and much praise should be given to the many investigators who are working on this phase of the subject. The widespread use of estrogenic substances in various gynecologic disorders has prompted an editorial comment⁷ on the work of Gemmell and Jeffcoate,⁸ who have observed the appearance of carcinoma of the cervix in 3 patients among 43 who were treated with estrogens for kraurosis vulvæ and senile vaginitis. The occurrence of these 3 cases cannot prove that carcinoma cervicis may be caused by estrogens, but they point out some practical lessons: (1) Every patient of menopausal or postmenopausal age, presenting symptoms of discharge, should be subjected to the most careful investigation to exclude carcinoma of the uterus, even when some lesion such as senile vaginitis appears to be the obvious cause. (2) Estrogens should be administered with caution if the patient has a lacerated or infected cervix or any other precancerous lesion. (3) Estrogens should probably not be administered to patients with a strong family history of malignant disease.

Diagnosis. In order to obtain the best results in the management of cancer of the cervix, it is essential to diagnose the disease in its early stage.

The iodine test which Schiller²² has popularized, will indicate suspicious areas in the cervix which should be subjected to biopsy. This test is based on the fact that the upper layers of the normal epithelium of the portio and the vagina contain rich masses of glycogen which disappear when the epithelium becomes cornified or changed by cancer. In the normal living tissue, the glycogen of the upper layers of cells is stained, in a few seconds, a deep mahogany brown by iodine in watery solution (Lugol's solution). A superficial area of early cancer, being devoid of glycogen, does not receive the stain and stands out startlingly white or pink against the deeply colored background of normal tissue. While the test is simple, it is not without its limitations. It appears to be completely reliable when it is clinically negative, that is to say, when all the tissues take the normal stain, therefore the test is specific in the *absence* of cancer, but there are several conditions that obscure the test, and with these the examiner should be thoroughly familiar. The stain does not take on glandular epithelium like that of the endocervix, hence an eversion would appear pink and an adenocarcinoma, which fortunately is rare, would not stain. Ulcerations and erosions have no epithelial covering of the squamous type, and hence do not stain. In areas of chronic cervicitis, the epithelium is often deficient in glycogen, taking a very light brown stain which blends with surrounding deeply staining tissue, instead of being sharply defined from it as in cases of cancer. It is also important to remember that the normal stain is prevented or obscured by a slight trauma such as that from tenacula or scrubbing with gauze. This is caused by the rubbing off of the upper layers of epithelium which contain the glycogen. The cervix and vagina of the hypoplastic and atrophic individual, stains lighter than the normal, but during pregnancy the stain is especially deep. Pus stains black, but living granulations do not take the stain, while mucus, blood and douche water obscure the reaction. Hyperkeratosis prevents the stain as in leukoplakia, lues, and exposed areas in prolapse. The test is of value only in cervical cancer and is not adapted to other superficial cancers, such as those of the vulva and skin in other parts of the body. This is due to the fact that the epidermis

of the portio and vagina is not cornified and that the upper layers of cells contain a special chemical type of glycogen. Schiller states that it is a mistake to carry out the test in suspicious cases only. We see carcinomas in women who never had leukorrhea, never had a discharge, in women with perfectly smooth cervixes and portios. He has discovered a number of early carcinomas in young women who came for backache, cystitis, or some other unrelated complaint. He believes that if we could examine all women once or twice a year, by the iodine test, then we would succeed in getting all carcinomas in the initial phase and all would have a definite possibility of cure.

Novak¹⁹ states, however, that both this test and the use of the colposcope are of rather limited value. Neither procedure is of the kind which can be expected to achieve adoption by the general profession, nor is this desirable. Considerable experience is necessary for proper interpretation with either method, and neither is of much value unless combined with biopsy and pathologic diagnosis, so that it is quite certain that the general practitioner will wish to transfer this responsibility to the specialist who is trained in such matters. Colposcopy, moreover, is a time-consuming procedure. The chief value of the Schiller test, even to the expert gynecologist, is to indicate the proper points for biopsy, though in the great majority of these cases the suspicious areas are apparent enough, sometimes pathetically so. The same statement may be made concerning the colposcope, so far as actual cancer is concerned. Novak does not believe that a good gynecologist who examines the cervix very carefully in a very good light, will overlook many cancers that the colposcope would reveal. Moreover, this procedure as well as the Schiller test, is obviously intended chiefly for the detection of the earliest cases, those in which there has been no bleeding, for the occurrence of the latter presupposes that ulceration has already begun. To pick up these very early cases, the colposcope would have to be used practically as a routine, which is almost out of the question in most clinics. In cases in which symptoms have already developed there is rarely any difficulty in finding the suspicious area with the naked eye. In the opinion of Martzloff,¹⁴ the iodine test is not specific for cancer or for areas of so-called probably beginning cancer. According to his experience, the overwhelming majority of unstained areas, including areas of leukoplakia, show no histologic evidence suggestive of probably beginning cancer. Small epithelial gland plugs, vermilion areas, a proportion of superficially situated nabothian follicle cysts, area of epithelial loss, either when superficial or, if complete, apparently when fibrin covers the base of the ulcer, epithelium involved in an underlying inflammatory process and particles of adherent inspissated secretion, together with other unexplained areas, fail to stain with the iodine. It follows that, if areas that do not stain with iodine are not interpreted with due reserve, they lead to endless confusion and alarm for the physician and unnecessary biopsy, cervical tinkering, and hysteria for the patient. He has not discovered a histologically proved area of probably beginning cancer with the iodine test, nor has the test proved to be of any more assistance than careful inspection with the unaided eye.

Since most authorities agree that the absolute diagnosis of cervical cancer must depend on the microscopic examination, usually of a biopsy specimen, Henriksen¹⁰ cautions that the amount of tissue for study must be sufficient to include not only the suspected area, but also some of the apparently normal tissue. For satisfactory interpretation of the histologic picture, an aggregate view of the changes must be obtained. Diag-

nosis based on the individual cellular changes is hazardous, especially when the tissue is scant in amount. One section from the area in doubt frequently misses the suspected process, while serial sections of the specimen will not uncommonly reveal the real nature of the lesion. The dangers of infection, dissemination or stimulation of the tumor growth, and hemorrhages, are apparently not as dangerous as they were once considered by many. In spite of any possible risks, the data obtained more than counterbalance them. That stimulation of the tumor growth occurs is not supported by the evidence now available; there is no proof that the growth is accelerated, and animal experiments show no change in the growth rate following trauma. Three days after taking a biopsy from a normal cervix, the wound is usually completely healed. Hemorrhage, except in advanced cases, rarely occurs, and at most amounts to only a slight venous ooze. An important factor in taking the biopsy is immediate fixation, for it has been shown that the alkaline secretions of the cervix bring about a definite fading of the nuclear particles, and thus the resultant microscopic picture is hazy. Immediate freezing and staining is the ideal method; but when permanent serial sections are desired from a small bit of tissue, this procedure is difficult and undependable except in the hands of an expert. Henriksen states that the divergence of opinion as to the diagnosis in very early carcinoma of the cervix is disheartening, many still seem to cling to the older concepts of cellular confusion so characteristic of the late stages. At the other extreme are those who scent malignancy wherever there is a departure from the accepted normal of cellular activity. In order to appreciate fully the pathology of the cervix, one must be especially equipped to diagnose the very early case. To attain this knowledge, one must possess a familiarity with all the various cellular changes, checked by careful follow-up studies in each case. Merely to call the changes "suspicious" or "doubtfully malignant" is of little aid to the clinician, who, if possible, wishes to be informed that the lesion is either benign or malignant. If the pathologist cannot decide either way, the responsibility reverts to the clinician; though when such doubt exists, the wise plan is often to defer active treatment until the question can be definitely settled, for such a slight delay will rarely endanger the patient.

Statistics show that in the United States 10% of patients with cancer of the cervix are nulliparous. In the Department of Gynecology (Univ. of Pa.) this percentage is about the same, as Tompkins²⁶ reports 53 cases in nulliparæ in a series of 505 patients treated. In a detailed tabulation of various phases of the disease, including race, age, extent when diagnosed, histologic type, treatment, and results, he found that this disease in the nulliparous differs in no respect from cancer in parous women. It is of passing interest to note that all of the cases in nulliparous patients were in white women and none were Jewish. In a clinical study of 940 cases of cancer of the cervix in Johns Hopkins Hospital, Henriksen¹¹ found that the average age was 46.1 years, while two-thirds of the cases occurred before the age of 50 years. Over 10% had never been pregnant. Bleeding from the vagina is the most frequent symptom, averaging 6 months before applying for treatment. Postcoital spotting occurred in less than 5%. Involvement of the urinary tract was present in 50% of the cases, with nocturia the most frequent complaint. Pregnancy has some influence on the growth of the tumor, while cervical laceration is a cardinal factor in producing chronic irritation. The average Hb. content was 75%, which is not much below average for normal women. Loss

of weight has no diagnostic value, as one-half of the patients had no loss. Pain rarely appears before parametrial invasion, unless due to associated pelvic lesions. In this series there were 22 cases in the cervical stump following subtotal hysterectomy, with an average lapse of 5 years. He assumes the growth to have been preëxistent to operation if it occurs within 2 years. The incidence of cancer of the stump in this series is less than 0.2%. Rectal invasion is rare, except in advanced cases. That cancer of the cervix is rare in adolescence is confirmed by the report of Bowing and McCullough,³ who point out that among 3000 patients with malignant neoplasms of the uterine cervix referred to the Mayo Clinic, only 1 instance of cancer in a patient less than 20 years of age was found. This occurred in a white girl of 13. The case emphasizes the need of making a careful manual and visual examination as well as microscopic and pathologic examination of any tissue which may be at all suspicious. They believe that, because of the rarity of the disease among patients 20 or less years of age, and of the difficulties encountered in making the diagnosis and the emphasis placed on the so-called cancer age, the diagnosis of cancer among young women is frequently confused or missed entirely. A search of the literature since 1862 revealed 25 cases of carcinoma of the uterine cervix in girls 20 years of age or younger.

Since leukoplakia is often considered to be a precancerous lesion, it is interesting to note that Schiller²³ states there is no causal relationship between para- or hyperkeratosis and carcinoma of the portio. From extensive material he could not find even 1 case of carcinoma that developed from a true keratosis. Cases with prolapse are excluded in this study; at best they disprove any relationship between carcinoma and cornification. In other parts of the body—mouth, lips, for example—cornification plays an important rôle in the etiology. These areas of leukoplakia do not warrant radical treatment, such as amputation of the portio advocated by some authors as a prophylaxis against possible malignancy. He found that these areas of leukoplakia remain for years without undergoing any changes. Malignant degeneration after 10 or 20 years cannot be excluded, but his observations point against it. If the histologic diagnosis is definitely established, a periodic examination is sufficient. Radical therapy is not justified. These areas of leukoplakia are to be grouped with the benign hyperkeratosis of the skin rather than with the leukoplakic areas of the mucosa of the mouth or larynx. As a means of making an early diagnosis in uterine cancer with a minimum of expense and annoyance to the patient, Papanicolaou and Traut²⁰ have advocated the study of vaginal smears. Cervical malignancy, in their experience, is revealed in vaginal smears by the appearance of characteristic cells. These are derived from the superficial layers of the tumor which undergo continual desquamation. These cells show great variety of form and size, much greater than that seen in sections of the tumor. Their distinctive features lie in their structural abnormalities. They do not fall into the categories of any of the cell types found in the vaginal fluid of normal women or of women having benign tumors or other pathologic lesions of the uterus. The most characteristic feature of the abnormal cells is the atypical form and structure of their nuclei. These often are very large, far surpassing normal size. The chromatin frequently shows a characteristic distribution in the form of conspicuous granules and of one or more small nucleoli. The cytoplasm also shows abnormal changes. It is often dense and hyperchromatic, particularly in the cells of the basal type. Such cells may appear either singly or in compact dark-staining

clusters. Their form and size vary greatly. Some of the basal cells assume elongate, spindle-like, triangular or ameboid forms. Basal cornified cells are not uncommon. Vacuolization of the cytoplasm is a characteristic feature. The vacuoles may be empty, or they may contain leukocytes, erythrocytes, cellular debris, or some pink-staining fluid. Sometimes the vacuoles occupy one side of the cell, while the dense cytoplasm and the nucleus are concentrated on the other side. A commonly found, very characteristic cell type is an extremely elongated one resembling a smooth muscle fiber. Long fibrous cells of this type are modified epithelial cells, and appear either isolated or in groups. Another deformed cell type which is often seen, is one having the form of a tadpole, with a spherical head containing the nucleus and a tail-like prolongation. The bulging of the heavier part which contains the nucleus is sometimes placed more centrally, causing a narrowing of the cell at both ends. Other cells attain very large sizes and acquire the most unusual forms. These "aberrant" cell types are numerous only in advanced cases of malignancy. They are relatively rare in the early stages of the disease, and a thorough search of several slides is often necessary before their presence can be established. For this reason, a negative diagnosis should always be made with extreme caution. Considering that, even in the advanced cases, the number of cells derived from the tumor forms only a small part of the total number of desquamated cells present within the vagina, it is natural to find the normal epithelial cells always in the majority. Blood elements are quite conspicuous in the vaginal smear of cervical malignancy. Erythrocytes are generally found in large numbers. Many show degeneration and have lost their hemoglobin. Fibrination is very pronounced. The complete absence of blood is so rare, even in the early stages, that it may be considered in favor of a negative diagnosis. The leukocytes are, as a rule, very numerous, more particularly in the advanced cases. After trying this method at the Massachusetts General Hospital, Meigs¹⁵ has been impressed with its accuracy, and believes it should be widely used. He states that a negative diagnosis should not be accepted as final in any patient with a suggestive history or examination. In any suspicious case, a negative smear must be checked by many more slides and by examination of biopsy material. A positive diagnosis does not mean that radical surgery or radiation should be undertaken, but indicates that confirmatory biopsies of the cervix or endometrium should be performed. Any patient with a positive vaginal smear who is without clinical evidence of cancer should be followed closely by repeated examinations and smears. The ease with which material for diagnosis can be obtained by this method makes the technique adaptable to office and out-patient department practice. However, since the recognition of cancer cells in the vaginal smear requires an experienced knowledge of cytology, it is suggested that there should be in every hospital a service for the interpretation of smears. It is his opinion that no longer can the vaginal smear be omitted from the routine examination of any female patient who is in the cancer age group.

Prognosis. Biopsy material from 728 cases of carcinoma of the cervix has been examined by Chambers,⁴ and 500 cases have been histologically graded based on the extent of differentiation and degree of cell activity and also on the general architecture of the growth. The results of treatment have been recorded, with special reference to the local area of the cancer at the primary site in relation to the histologic type. The highest percentage of local cures has been obtained in the transitional type of squamous cancer (73.8%) and in the adenocarcinomata (72.9%), but

none of the histologic grades show a difference of more than 15% in either local cure or in the number of 3-year survivors. There is no evidence that adenocarcinomata are insensitive to irradiation. Following a careful analysis of the survival rates of patients following irradiation, Meigs and Jaffe¹⁷ have found that the first 2 years are the serious years for patients with cancer of the cervix, for in the 3rd and 4th years, respectively, less than 9% of the total number of cases, not including the survivors, died. In the 5th year not over 5% died, and in the 6th, 7th, and 8th years not over 2%. Thus it is evident from these various charts that end-results in a series of cases of cancer of the cervix treated by radium or radium and Roentgen ray can be predicted by subtracting 10% of the total number for the 3rd year, 10% for the 4th year, and 5% for the 5th year, and results up to the 8th year by subtracting 2% for each of the next 3 years. This should be of great value. Thus, if at the end of the 2nd year in a group of 100 patients, 54% are alive, 10% may be subtracted for each of the next 2 years, leaving 34% and for the 5th year 5%, leaving 29% of predicted 5-year survivors. Thus, final results will be within a 5% error. Such mathematical maneuvers are of enormous value, for the therapist can satisfy himself of his expected results after a follow-up of 2 years, and certainly after a follow-up of 3 years. It is obvious that most of the deaths occur in the first 2 years, and most patients who have no obvious disease at the end of 2 years have a good chance for recovery. They state that it is only necessary to follow our cases for 3 years following treatment, and then by deducting 15% the 5-year end-results can be predicted. Therefore, it is unnecessary to wait for 5 years following treatment before reporting a group of cases or to change a method of treatment. For those patients who have survived the 5-year period, the report of Kimbrough and Tompkins¹³ based upon 304 patients treated at the Hosp. of the Univ. of Pa. is helpful. They found that 23.3% of the patients survived 5 or more years, and 18.7% of the original group lived more than 10 years after treatment. In other words, four-fifths of those who survived 5 years lived at least 10 years after treatment. Based on her observations of over 900 cases of cancer of the cervix at the Marie Curie Hospital in London, Goldschneider⁹ states that the occurrence of pyrexia in the course of radium treatment is an unfavorable development and usually indicates an increased immediate mortality as well as a reduction in the number of 5-year cures.

Radiotherapy. For many years irradiation has been advocated by most gynecologists as the safest and best method of treatment, but lately there has been a trend back toward operative treatment. In order to compare these 2 types of treatment, Jones and Jones¹² have reviewed a selected group of 36 cases of early carcinomas of the cervix treated with panhysterectomy and compared the results with 704 unselected cases in all stages, treated with radiation. Although irradiation has been demonstrated by numerous observers over a period of years to be more satisfactory than panhysterectomy for the average case of cervix carcinoma, it is the opinion of many gynecologists and general surgeons that operation is a satisfactory method of therapy for very early cases. That panhysterectomy is commonly selected in such cases is indicated by the fact that, in their experience, for every 10 patients with primary carcinoma of the cervix there is 1 admitted for treatment of a recurrence after operation. During the years 1927 to 1937, 36 patients with early carcinoma of the cervix were carefully selected for operation at the Johns Hopkins Hospital. In spite of this careful selection, a 5-year cure rate of only 41% was

obtained. This does not compare well with the cure rate of 57% obtained by irradiation with less favorable material. It has, therefore, been concluded that as a practical therapeutic procedure for early carcinoma of the cervix, panhysterectomy is an unsatisfactory method of therapy. Irradiation is the treatment of choice.

While the present study strongly suggests that operation is not the method of choice in early Stage 1 cases, especially in the transitional and spindle cell groups, it does not at all indicate that the "accidental" and preinvasive lesions should not be operated on. In the 36 cases of the operative series herein reported, 5 belong to this group. All these patients are living except 1, who died of postoperative shock. With the information at hand, the question of operation or irradiation cannot be definitely decided for this group. In a more general consideration of the selection of type of therapy for these early cases of carcinoma of the cervix, it is worth noting that, although the lesion in several instances was thought to be of the earliest, there was found on examination of the gross operative specimen, a large intracervical nodule of cancer. For this reason, and because of the experience considered in this paper with slightly more advanced squamous cell lesions, they feel that irradiation will prove more satisfactory for the entire squamous cell group, including the "accidentally" discovered and preinvasive lesions. If radium is selected as the method of treatment, full dosage should be employed, because early lesions of the cervix may be more extensive than clinical examination can indicate.

While the application of radium under ordinary conditions is a comparatively simple procedure, there are many complications which may occur. In presenting some of these, Cutler⁶ mentions the condition which renders it difficult and sometimes impossible to introduce radium safely into the cervical canal, namely, occlusion of the canal by the growth. The danger of perforation in an effort to locate the cervical canal under these circumstances is well known. Experience has demonstrated the importance of avoiding this danger. This can be accomplished by initiating the treatment with external and vaginal radiation. The regression of the lesion following these procedures, with rare exceptions, results in a disappearance of the occlusion so that the cervical canal can be located without undue trauma and with no danger of perforation.

Pyometra may be divided into 3 groups: (1) Early pyometra due to occlusion of the cervical canal and appearing toward the end or within several weeks after radiation. This complication should always be considered and recognized as early as possible. Dilatation of the cervical canal and drainage frequently terminates this complication. (2) Late pyometra occurs from 1 to several years after treatment. The condition has to be differentiated from recurrence. The treatment is the same as for early pyometra. Occurring long after treatment, the diagnosis is more likely to be missed. (3) Late infectious parametritis, a complication that arises usually 1 to 3 years after radiation treatment. It may be due to a reactivation of an old latent infection or to a new infection which becomes localized in tissues of a lowered resistance. This inflammatory complication must be differentiated from recurrent cancerous disease.

Infection during the process of irradiation is by far the most important complication associated with the radiotherapy of the cancer of the cervix, the 2% mortality charged against this procedure being due almost exclusively to the activation of hemolytic streptococci by the radiation. In an effort to determine the virulence of the microorganisms, Ruge devised

a clinical test which has been amplified by Philipp. The Ruge-Philipp test determines the ability of the patient's microorganisms to grow in a medium containing the patient's own blood. If the bacteria grow and multiply they are considered virulent. If they fail to grow or if they diminish in number they are considered of uncertain virulence. With this classification it was found that radiation treatment in the presence of avirulent streptococci resulted in 1 death (2%). One patient developed severe complications and 48 had a smooth convalescence. Of 22 carriers of virulent streptococci, 5 (19%) died, 8 showed severe complications, and 13 showed a smooth convalescence. Many procedures have been advocated to combat this complication. Antiseptic douches, hypertonic salt solutions, copper salts, vaccines, autovaccination and antistreptococcus serum have been recommended. Since the introduction of sulfanilamide and its derivatives, several reports have appeared in the literature indicating their value in the treatment of these infections.

Intestinal injuries resulting from irradiation have been studied by Aldridge,¹ who states that they usually manifest themselves with the onset of intestinal symptoms, such as abdominal pain, frequent bowel movements, rectal tenesmus, and passage of varying amounts of blood and mucus by rectum. In some cases, the initial symptoms are those of intestinal obstruction, that is, abdominal pain, anorexia, nausea, vomiting, and obstipation or obstipation alternating with diarrhea. When these symptoms appear, they may be due to a temporary partial intestinal obstruction caused by hyperemia, edema, and spasm of the bowel at the site of an intestinal ulcer, or to a true organic stricture resulting from the formation and contraction of scar tissue as Nature attempts to heal the injured bowel. Symptoms of an intestinal injury may develop at any time from immediately following irradiation therapy to within several months or years later. Acute proctosigmoiditis is the mildest form of intestinal injury observed as a result of the secondary effects of irradiation therapy for uterine carcinoma. Characteristic intestinal symptoms appearing during the course of the treatment or soon after its completion give the first warning of the presence of such an injury. The symptoms include abdominal pain, diarrhea, rectal tenesmus and the passage of small amounts of blood and mucus by rectum. Examination will reveal a typical localized inflammatory process involving the anterior wall of the rectum and distal end of the sigmoid at about the level of the cervix. The mucous membrane over the area is soft to palpation, intensely hyperemic in appearance or edematous with considerable mucous secretion over its surface. Trauma of the palpating finger or passage of a proctoscope readily induces slight bleeding. With a bland diet and suitable palliative treatment, these mild injuries heal spontaneously and symptoms disappear soon after termination of irradiation therapy, leaving no evidence of damage to the mucosa or wall of the intestine. When injury to the bowel is more severe than that which causes an acute proctitis, ulceration of the intestine usually occurs. Although ulcerative lesions have been observed on both the rectum and sigmoid, the usual location for their development is on the anterior wall of the bowel at about the level of the cervix or at about 8 to 10 cm. from the anus. In a small percentage of these cases, perforation of the bowel occurs into the peritoneal cavity, causing peritonitis; into the vagina, producing rectovaginal fistulas; or into the perirectal tissues, giving rise to ischiorectal abscesses requiring incision and drainage. Ulcerative lesions make their appearance at any time from soon after termination of irradiation therapy to within several weeks or months later.

They tend to heal slowly with separation of sloughs from their bases and inward growth of the surrounding healthy intestinal mucosa. Injuries resulting in acute proctitis and ulcerative lesions appear to be confined essentially to the mucosa and wall of the intestine itself and have been referred to as "intrinsic lesions." There are a few other cases in which the primary injury appears to have involved the perirectal tissues. The characteristic tissue reaction following such injuries is the formation of a diffuse mass of fibrous tissue involving all the pelvic structures below the uterocervical junction and extending upward and backward to the second or third sacral vertebra. This type of tissue reaction to irradiation referred to as an "extrinsic lesion" produces a pelvic condition which is difficult to differentiate from the so-called "frozen pelvis" caused by massive invasion of all pelvic structures by malignancy. It may be associated with an ulcerative lesion of the bowel. As healing of this type of injury progresses, the lower bowel is likely to be distorted by contraction of the fibrous tissue and by external pressure causing intestinal obstruction. That this condition is not a rare one is shown by the report from the Mayo Clinic by Randall and Buie,²¹ who present data on 88 cases in which significant symptoms led to proctoscopic examination and a diagnosis of factitial changes in the rectum following radiation therapy. These symptoms, in order of frequency, were most commonly bleeding from the rectum, mucous discharge, and constipation. Other complaints that were made less frequently were of abdominal cramps, decrease in the size of the stool, and tenesmus. The average time that elapsed between the initial course of treatment and the appearance of symptoms was 10 months. Ten patients complained of various rectal symptoms that commenced immediately after treatment, and 3 patients noted the first symptom, bleeding from the rectum, 38, 40 and 48 months, respectively, after the initial treatment. Except in those few cases in which ulceration is sufficient to lead to formation of fistula, or in the occasional case wherein actual involvement of the rectovaginal septum by the malignant process is responsible for breakdown of the tissues, healing will take place, providing the patient survives the malignancy for a sufficient time. Healing is accompanied by scarring, occasionally some reduction in the size of the lumen of the rectum and by telangiectasis which usually produces bleeding from the rectum. Usually the patients can be taught proper care of the rectum. It should be explained to them that time is one of the most necessary factors to be considered, and that treatment usually is prolonged. The patient should take a warm, cleansing enema after each defecation in order to keep the rectum as free from fecal matter as possible. She is then instructed to inject 2 fluidounces (60 cc.) of warm hamamelis water (witch hazel), to be retained until the next movement of the bowel. Often the injection of 2 fluidounces of warm olive or mineral oil before retiring is of benefit. A bland diet, reinforced with some substitutes to furnish bulk, such as are now available, allows a soft stool free from irritating particles. Caustic medicaments should not be applied.

Following his experiences with nearly 50 cases of rectal ulceration, or as he calls it "pseudo-carcinoma of the rectum" following cervical irradiation, Todd²⁵ states that colostomy is frequently necessary, especially if stenosis, hemorrhage or severe pain are prominent symptoms. In order to prevent the occurrence of rectal ulceration, he gives several suggestions which sound valuable. He states that in order to utilize to the full the possibility of obtaining distance protection from the rectum, all vaginal applications of radium should be made with the patient in the knee-chest

position. The lips of the cervix, or a portion of the growth, should be sutured over the intrauterine tube to ensure that it does not slip into the vagina, or alternatively, a special type of applicator devised to prevent this complication, should be used. A locking device for the vaginal applicators should be used in order to prevent slipping and approximation. Repeated skiagraphs should be made during treatment to ensure that the position of the applicators remains constant; if slipping occurs, it is recognized, and the radium can be removed before damage is done. In the presence of retroversion, the intrauterine dose should be reduced, or the distal needle omitted in subsequent applications. A special applicator should be used during Roentgen ray treatment to limit the amount of radiation delivered to the rectum. Routine blood counts during treatment will demonstrate any marked constitutional effect due to the radiation. A pronounced lymphopenia indicates the advisability of stopping treatment. Preliminary proctoscopy will show whether or not the rectal mucosa is normal before radiation. Should rectal symptoms occur during treatment, proctoscopy will show whether or not there is any excessive reaction, and will decide whether the continuance of treatment is safe.

Operative Treatment. As previously stated, there is a tendency toward the resumption of operative treatment in this country, but in Europe there have always been some gynecologists who favored the surgical operation in spite of the favorable results others were achieving with irradiation. In 1936, Bonney² did his 500th Wertheim operation during a period of 34 years. In the operation he removes nearly all of the vagina, the uterus, appendages, iliac and obturator glands, and as much of the parametrium as possible. In addition to marked extension of the growth, operation may be contraindicated on account of grave diseases of the heart, lungs or kidneys, severe diabetes or gross adiposity. In such cases he advocates radium. He does not use radium preoperatively nor Roentgen ray postoperatively. Of the 500 cases, 201 were well after 5 years, 193 recurred before 5 years, 36 were not followed or died of other diseases, and 70 died of operation. Thus the absolute cure is 40 %, the relative salvage is 43 % for 5-year statistics. About 65 % of recurrences occurred within 2 years after operation. Recurrences were treated by irradiation, but uniformly without success. He considers recurrence after a Wertheim operation as practically incurable by any means. The operative mortality rate of 14 % was largely due to shock. In about 40 % of the cases the regional glands were involved, and in these the 5-year cure rate was only 23 %, as opposed to the cases free from gland involvement and where the cure rate reached 58 %. Similarly, the operative mortality was only 10 % in the gland-free cases against 20 % for the gland involved group. Vesical fistula occurred 8 times, 1 cured by operation, 1 closed spontaneously, 4 remained open until death and 2 operated with death. Ureteral fistula—8 cases, 3 closed spontaneously, 2 cured by grafting ureter to bladder, and 3 remained open until death. Ureter divided accidentally only once, but intentionally 12 times with implantations in the bladder, of whom 5 died of operation, 2 of recurrence, 2 are 10-year cures, 1 a 5-year cure and 1 died of coronary thrombosis years after the operation. He admits that radiation gives results as good as surgery with much less risk, and states that no surgeon should undertake the operation unless he has served an apprenticeship in it, as it is the most difficult of gynecologic operations.

In order to determine the status of therapy in cervical cancer in Central Europe, Mikulicz-Radecki¹⁸ collected statistics from 11 important clinics, embracing cases treated between the years 1919 and 1926, only a few of

these statistics having been previously reported. The combined series totaled 5455 cases. Of these, 34.8% were operated upon and usually supplemented by postoperative irradiation. The remainder of the series was treated by irradiation alone, except for 5% which were hopelessly inoperable and were not treated at all. Of the entire series, 24.5% were cured, which is the best absolute cure rate thus far published in such a large series. One clinic (Stoeckel) reached the very high rate of 36.5% of absolute cures. It should be borne in mind that absolute cures represent the percentage of all patients seen and not merely the percentage of those treated. Of course, in this series, since all but 5% were treated, the absolute and relative cure rates would not be very different. Armed with such statistics he states that such "elective therapy," that is selecting the type of treatment for the individual patient is the best method of treatment. This means that from 20 to 40% of the patients should have the radical operation with the greatest possible removal of parametrial tissue. He believes that the radical operation is superior to the irradiation alone, but simple hysterectomy is a useless procedure. Abdominal and vaginal radical operation give comparable end-results, but the mortality of the vaginal operation is lower principally because of the less chance of infection as a complication. Any operative procedure, however, should be reserved for the good risk patient if the mortality is to be kept low. These patients should have Roentgen irradiation postoperatively, but in cases where satisfactory removal of the parametrium is doubtful, radium is applied in the parametrial and pararectal spaces. Preoperative irradiation is employed in cases in which it is hoped to bring them from the doubtful to the operable class, but as a routine treatment in all operable cases it only wastes valuable time, and its value as a preventive of postoperative infection has not been proven. All inoperable cases should be treated with intensive radium or Roentgen irradiation.

Crossen⁶ states his views on the subject editorially by saying, in his book "Operative Gynecology," that he expects to retain a description of the radical operation because of its historical importance in the development of the effective treatment of this disease. However, as a method of choice in the handling of carcinoma of the cervix today, radical operation as opposed to irradiation is a back number, an obsolete method. He feels that it will probably take 10 years for this knowledge to permeate the profession and bring to the patients generally the benefits of a most effective treatment, especially if journals and books push the operation. Briefly stated, he believes that the successful care of a patient with carcinoma of the cervix is based upon an organized combination of expert services. The crucial point of attack is not in the uterus but in cancer cells along the pelvic wall. It is these outlying cells that must be reached and destroyed or recurrence is certain. Irradiation is the most important factor in attaining success in this concerted attack on the outlying cancer cells. There are exceptional conditions in which operative work with the knife also may be advisable, but, wherever used, operation should supplement irradiation and not displace it. Too many of these patients are still being treated with half-way measures, with operations that never reach the outlying cancer cells, and inefficient irradiation treatments that carry no devitalization into the distant cervical zone. Meigs¹⁶ gives 5 reasons why he has resumed the operative treatment of cervical cancer. They are as follows: (1) if the cervix has been removed there is no chance for a recurrence in it; (2) if the cervix has been removed no cervical cancer can re-grow in it as a recurrence; (3) certain cancers of the cervix are radiation-resistant—a fact proved at the Pondville Hospital, where multi-

ple biopsies are performed at the time the Roentgen ray and radium treatment are being carried out; (4) there will be less damage to the bowel if surgery is undertaken; (5) from the work of both Bonney and Taussig it is obvious that patients with lymph node metastases can be cured by surgery in some instances, and the author believes that it is not possible to cure, with radiation, cancer in lymph nodes deep in the pelvis. The surgery must be limited to certain types of patients; ideally they should be thin, young, in good health, and have an early growth. One other group has been operated upon and will be discussed separately in the statistics and results. These are the patients in whom one or two radiation attempts at cure have failed. These cases are non-elective and are "must" cases, and the results would be expected to be poor, and they are.

The preparation of the patient for operation is very important. This consists of admitting the patient to the hospital 4 to 5 days before the operation is to be done. The blood chemistry must be brought to normal, vitamins are supplied in large amounts to arrive as far as possible at a normal level, and blood transfusions are commonly given. Two days before operation, the patient is started on 1 gm. of sulfadiazine every 4 hours. The blood level has been determined in the beginning and is usually found at 6 to 8 mg. per 100 cc. Lately, the sulfadiazine has been given without determination of the level. At operation, 4 gm. of sulfanilamide are placed in the large pelvic defect under the new peritoneal floor. Sulfadiazine is continued by mouth as soon as the patient can take it, and is continued for 7 days after operation. Of 47 selected cases, none has died, an operative mortality of zero. It was essential in this series that the mortality be low, for the results with radium in the radiated cases are so good that a 10 to 20% would prohibit surgery. A mortality of 0%, or a very low mortality, gives the operator a feeling that at least he is as well off as is the radiologist in treating this type of disease. The most significant complications are difficulties with the urinary tract. Cystitis, dilated ureters, and hydronephroses are the rule after operation, not the exception. In most cases, an intravenous pyelogram taken before discharge will show large ureters and kidney pelves, but this condition will clear up. Occasionally, patients have difficulty in voiding or emptying the bladder due to injury to the sympathetic or parasympathetic nerves. In 5 (10.6%) of the 47 cases, ureteral fistulas developed, which in all cases will mean ultimate nephrectomy. This is a serious complication, but not a fatal one. In 1 patient with a huge tumor, both ureters were injured. There have been no vesicovaginal fistulas. The bladder was opened once and it was closed without any ill-effect. In 8 (17%) cases, lymph nodes were found to be positive; iliac nodes in 4, ureteral nodes in 1, and obturator nodes in 5. It is extremely important, however, to realize that 8 of these patients with very early lesions would have eventually died if radiation had been used. In this group with positive nodes, only 1 patient has succumbed so far. Of the 6 patients with recurrent disease or non-elective cases in whom operation was forced upon the surgeon, 5 have died, and 1 died of general peritonitis after operation. This is the only death in the series and, adding the groups together, makes 1 death in 53 patients (1.9%). It is interesting to note, and of real importance, that the patient who died was the only one of the entire series who was not prepared with a sulfonamide. Enough time has not elapsed to make the end-results of any value, but 5 are alive over 3 years; 4 over 2 years; 13 over 1 year; and the others for varying months under 1 year. Of the elective cases, 3 died of cancer. One died of cancer of the lung 2 years and 2 months after operation, and 1 died of generalized metastases

throughout the body. He believes that surgery in selected cases is a better way to treat cervical cancer than is radiation. The experience of the patients who have had both methods of treatment has always been that the surgery was much easier to tolerate than the radiation. Surgery of this extensive type can be done safely if we take advantage of all the precautions of modern surgery. The preparation of the patient, the maintenance of good diet, hygiene, the correction of blood chemistry, the use of transfusion, and especially the use of sulfonamides make for safer surgery. This series demonstrates that, in the hands of one surgeon, nearly 50 selected patients were put through a grueling operative procedure without mortality. If it were not for injury of the ureter, it would probably be safe to say that this operation is better than radiation, but a ureteral injury of 10% in early cervical cancer is too large.

For over 10 years Taussig²⁴ has practiced the removal of the iliac lymph glands in addition to irradiation of the primary tumor in Group 2 cancer of the cervix, and has done 175 of these operations. He believes that the Wertheim operation with gland removal is the best procedure in the majority of early Group 1 cases. For persons untrained in the technique of the radical hysterectomy, he believes it safer and better to do the lymph gland operation with radiation of the cervix rather than an extensive Wertheim procedure. Hemorrhage was not infrequently an operative complication, especially since wider dissections have been practiced. In 11 patients, the hemorrhage was disturbing, but in no case was it fatal. Almost always the bleeding originated in the plexus of veins at the point where the internal iliac vein divides into its branches. These veins are very friable. In the first cases, he tried to catch these veins with forceps and attempted to pass a needle with ligature around them. Invariably the needle would puncture another vein and the bleeding increased. Three of the earlier cases of severe hemorrhage were left open, with clamps and a gauze pack to control the bleeding. Clamps and gauze were removed in 48 to 72 hours. Recently the cases have been handled far more successfully by a firm gauze pack with a strip of the rectus abdominis muscle applied against the bleeding area to promote coagulation. In 15 to 20 minutes the bleeding was usually controlled, and the operation could be concluded. In 2 cases a small gauze pack was left in the broad ligament for 48 hours. In the remaining cases, the bleeding was fully controlled and the pack removed before closure. This excessive bleeding can usually be avoided by more gentle manipulations in the deeper portions of the broad ligament. Injuries to important viscera or nerves are rare. The bladder is out of the operative field. The ureter must be watched, especially if large cancerous glands are present, as it may then be adherent to them and stripped off of its normal attachment to the posterior sheath of the peritoneum. Once he ligated the ureter but without harmful result to the patient. Once the obturator nerve was resected with an adherent obturator gland, but produced only temporary discomfort.

The percentage of 5-year survival was over 15% better in patients who had the additional procedure of iliac lymphadenectomy; or, to put it from the standpoint of patients saved, over 68% additional were saved by this operation.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF OCTOBER 17, 1944

The Effect of Quinones on Blood Pressure in Hypertensive Rats. W. M. ZIEGLER and HENRY SCHWARZ (Philadelphia Institute for Medical Research, Phila. Gen. Hosp.). In a recent study Henry Schwarz and W. M. Ziegler found that 2-methyl-1,4-naphthoquinone considerably lowers the blood pressure of rats made hypertensive by silk perinephritis, and that a hydroquinone compound with similar vitamin K activity (*e. g.*, Synkayvite) does not produce any depression of blood pressure at all. (*Proc. Soc. Exp. Biol. and Med.*, 55, 160, 1944.) The present studies were undertaken in order to investigate whether a definite chemical structure of p. quinones might be essential for their effect on blood pressure in hypertension. We also wanted to examine whether hydroquinones act differently, as was to be assumed from the 1 compound investigated. Our studies were performed in rats made hypertensive by wrapping both kidneys with silk. Eighteen different compounds, 14 quinones and 4 hydroquinones, many of them prepared in our laboratory, were assayed. The substances were dissolved in oil and given daily by intramuscular injection. The blood pressure was measured before, throughout and after the whole period of the experiment. Altogether 90 animals were used for the assays. The results of these studies are given in the following table:

ACTIVE DEPRESSORS

Toluquinone
p. Xyloquinone
m-Xyloquinone
Thymoquinone
-Naphthoquinone
Menadiione
2-ethyl-1,4-Naphthoquinone

INACTIVE

Quinone
2,3-dimethyl-Benzoquinone
Duroquinone
2,5-diethyl-Benzoquinone
Anthraquinone
Tetrahydro-Naphthoquinone
2,3-dimethyl-Naphthoquinone
Toluhydroquinone
m-Xylohydroquinone
Thymohydroquinone
Synkayvite

From these studies it becomes clear that 1 hydrogen and 1 alkyl group are essential for the depressor effect of quinones in experimental hypertension. These radicals have to be at an essential place, *e. g.*, on the same half of the oxidized benzene ring imaginarily divided in a vertical direction.

The type of the alkyl group might be of importance since the 2,5-diethylbenzoquinone does not show any effectiveness, while the corresponding p. Xyloquinone is a powerful depressor. The effectiveness of the 2-ethyl-1, 4-Naphthoquinone might probably be explained by a change of the ethyl into a methyl group in the body. The -Naphthoquinone, which also lowers the blood pressure, is the only compound so far tested which does not show the essential structure. It has to be pointed out, however, that this substance is relatively toxic and that the difference between the effective and toxic doses is relatively small in this case.

All of the 4 hydroquinone compounds tested were ineffective. Since at least for the Synkayvite a transformation of the hydroquinone into quinone has been proved recently for normal animals (D. A. Richert, *J. Biol. Chem.*, vol 154, 1944) it might be assumed that in experimental hypertension the oxidative transformation of hydroquinones into quinones is disturbed.

A Bacteriolytic Substance Contained Within a Purified Bacterial Virus.

T. F. ANDERSON (Johnson Foundation, Univ. of Penna.). Centrifugally purified preparations of the tadpole-shaped bacterial virus γ have been found to lyse suspension of the host (*E. coli* strain B) which have received so much ultraviolet irradiation that multiplication of the virus does not occur. Moreover, such lysis proceeds immediately upon addition of virus to the host cells; this is in contrast to lysis of normal cells by virus which occurs only after a definite time interval in which the virus multiplies within the host cell. It thus appears that the virus has the ability to dissolve some substance or substances which hold heavily irradiated cells together. Disintegration of the virus particles by sonic vibration or by ultraviolet light fails to destroy the lytic activity, but rather enhances it.

Indeed, ultraviolet irradiation of the virus frees the lytic principle from the sedimentable material, for the activity of irradiated preparations remains in the supernatant even after centrifugation at 100,000 x gravity for 1 hour. The virus lysin may be similar to lysozyme for this enzyme also lyses heavily irradiated cells of *E. coli* B. However, the virus lysin appeared to be more specific in its action, for it exhibits no visible effect on *M. lysodeikticus* on which lysozyme is most active. Like lysozyme it is inactivated by 0.00001 N iodine and is not inactivated by 0.125 M Na_2AsO_3 , 0.06 M NaN_3 or 0.125 N Na_2SO_3 . MgCl_2 at 0.05 N inhibits its action either by an action on it or on its substrate.

The Quantitative Determination of Cerebral Blood Flow in Man by the Use of Nitrous Oxide in Low Concentrations.

SEYMOUR S. KETY and CARL F. SCHMIDT (Dept. of Pharmacol., Univ. of Penna., and Med. Services, Phila. Gen. Hosp.). The proposed method is an application of the familiar Fick principle to the brain during its absorption of an indifferent gas from the blood passing through it. The relationships implicit in this principle may be expressed thus: cerebral blood flow (as cc. of blood per unit mass of brain tissue over any time period) is equal to the quantity of any gas taken up by unit mass of brain tissue during the same interval, divided by the quantity of that gas lost per cc. of blood during that period.

The experimental procedure involves the administration by inhalation of a gas mixture containing nitrous oxide (15%), in oxygen or a mixture of oxygen (21%) and nitrogen (64%). From needles inserted in the internal jugular vein and the femoral artery simultaneous pairs of blood samples are taken at 2, 4, 6 and 10 minutes after the onset of inhalation

of the mixture. From the respective nitrous oxide concentrations it is possible to calculate the integral of the nitrous oxide arteriovenous difference over the 10-minute period which represents the quantity of gas lost to the brain per unit volume of blood during that time. The quantity of nitrous oxide taken up by the brain in that time is calculated from the internal jugular concentration of nitrous oxide in the 10-minute sample and from the partition coefficient of nitrous oxide between brain and blood.

The theoretical steps involved in this derivation have been subjected to experimental verification in monkeys, dogs and human subjects. Final proof of the validity of the method has been obtained by a comparison with values for cerebral blood flow obtained simultaneously in rhesus monkeys by direct measurement using the bubble flow meter (*Am. J. Physiol.*, **138**, 421, 1943). In 9 such comparisons the mean deviation between the two methods was $\pm 10\%$.

By means of this method cerebral blood flow and cerebral oxygen consumption have been measured in 8 human subjects representing 2 normal adults and 6 patients with various diseases. The values have fallen within a fairly close range. In the 2 normal subjects cerebral blood flow was 66 and 56 cc./100 gm./minute and cerebral oxygen consumption 4.4 and 3.7 cc./100 gm./minute respectively. These values are in excellent agreement with the averages recently reported for the rhesus monkey by the use of the bubble flow meter: cerebral blood flow 47 cc./100 gm./minute and cerebral oxygen consumption 3.7 cc./100 gm./minute (*AM. J. MED. SCI.*, **207**, 813, 1944). For a normal human brain weighing 1300 gm. the values obtained by the nitrous oxide method would yield a total cerebral blood flow of 780 cc./minute and a cerebral oxygen consumption of 52 cc./minute.

Even 15% nitrous oxide is not completely inert physiologically and might conceivably influence cerebral blood flow. This disadvantage may be overcome by the use of a radioactive inert gas instead of nitrous oxide.

A Further Study of the Innervation of the Pancreas—The Action of Drugs of the Atropine Group. J. E. THOMAS and J. O. CRIDER (Laboratory of Physiology of the Jefferson Medical College). The secretory response of the pancreas to peptone, soap, or HCl in the intestine or to intravenous secretin was studied in unanesthetized dogs before and after administration of atropine or hyoscyamine. The usual dose of atropine (sulfate) was 0.2 mg. and of hyoscyamine (hydrobromide) was 0.1 mg. per kilogram.

The specific gravity and total N (mg./cc.) of the pancreatic juice were decreased by the action of these drugs regardless of the stimulus used to promote secretion. When the stimulus was soap, HCl, or secretin the volume of the secretion and total nitrogen output were also reduced. When the stimulus was peptone an increase in volume of secretion usually followed administration of either drug; the effect on total nitrogen output was not constant but an increase was common.

The fact that the parasympathetic depressants decrease the response to secretin is surprising and contrary to results obtained by others in anesthetized animals. Probably "tonic" cholinergic reflexes normally augment the response to secretin in unanesthetized animals. The results with soap and HCl indicate that these agents stimulate the pancreas in part through a nervous mechanism. The experiments provide no basis for conclusions regarding the mechanism through which peptone stimulates the pancreas.

BOOK REVIEWS AND NOTICES

TECHNIC OF ELECTROTHERAPY AND ITS PHYSICAL AND PHYSIOLOGICAL BASIS. By STAFFORD L. OSBORNE, M.S., PH.D., Assistant Professor, Department of Physical Therapy, Northwestern Univ. Med. School, and HAROLD J. HOLMQUEST, B.S., B.S.(M.E.), Lecturer in Applied Physics, Department of Physical Therapy, Northwestern Univ. Med. School, Chicago. Pp. 780; 240 figs.; having 293 illus., 72 tables. Springfield, Ill.: Charles C Thomas, 1944. Price, \$7.50.

THIS new work is the outgrowth of numerous requests from the authors' students. It is divided into 4 parts: direct current, electrical stimulation of muscle, radiation, and high-frequency currents. It is one of those not-so-common books which serve not only as a reference text but also as a laboratory guide and manual. The first part in particular is well designed for the latter purpose. A short historical survey precedes many of the sections. Fundamental principles are outlined in simple form for the benefit of beginners; foot-notes, tables, and mathematical formulæ are appended for the more advanced students. References to literature appear at the bottom of pages.

There is a tendency to some unevenness in the space allotted to various subjects; a discussion of coal tar as a sensitizing agent prior to the use of ultraviolet occupies 2 pages while the biologic effects of ultraviolet occupy a bare 13 pages. The magazine *Time* attains bibliographic stature, as in the discussion of fluorescence; a "personal communication" from the authors whose work was cited would have been more appropriate. Over 400 pages are devoted to the portion dealing with high-frequency currents; the discussion of artificial fever is excellent. Short summaries at the end of sections are an added feature. Illustrations are clearly reproduced, numerous and well chosen. Type face, setting, and a thin glossy paper make the whole "eye easy" and very compact.

This contribution to an important aspect of physical medicine is warmly recommended. M. B.

TECHNICAL METHODS FOR THE TECHNICIAN. By ANSON LEE BROWN, A.B., M.D., Director of Dr. Brown's Clinical Laboratory and Dr. Brown's School for Technicians, Columbus, Ohio. Pp. 706. Third Ed. 229 figs. Published by the Author, 1944. Price, \$10.00.

THIS text comes from the Author's school for technicians. In content and style it seems designed for the average high school graduate lacking much background in science. The vocabulary is simple; elementary procedures are described in detail; technical terms are defined in abundance; and review questions are listed at the end of each chapter. Good instructions are given for such beginner problems as operation of a microscope, handling of reagents, chemical filtration, weighing with a balance, use of a counting chamber and taking of a basal metabolism test. There are many good line illustrations and several color plates of the blood cells and of blood groupings. Directions are offered for performing 8 different serologic tests for syphilis, including an original micro-precipitation technique, "presented for the first time," based on extracted powdered beef testicle as the antigen. The blood chemistry chapter is well done, but the sections on feces examination, gastric analysis and semen study are inadequate. Bacteriology and electrocardiography are not discussed. Erroneous statements abound, such as: "the slightest trace of albumin in the urine is considered abnormal" (!); "the normal specific gravity for urine is usually given as 1.012 to 1.020" (a narrow nephritic range!); when doing Benedict's test for sugar in urine "heat for not over 10 to 15 min-

utes" (much too long!); with the Westergren blood sedimentation test, "above 6 or 7 mm. is pathological" (customary accepted limits are about 15 mm. for men, 20 mm. for women). No space is given to pentosuria, recognition of the cells of infectious mononucleosis, the dark-field test for spirochetes, and other valuable methods. This book may find some application in the office of a doctor himself skilled in basic principles, who is teaching his secretary to assist in laboratory procedures, but it cannot be recommended to physicians or technicians as an authoritative reference.

I. W.

MANUAL OF PSYCHOLOGICAL MEDICINE. For Practicioners and Students.

By A. F. TREGOLD, M.D., F.R.C.P., F.R.S.E., Consulting Physician to Univ. College Hosp., London Lecturer on Mental Deficiency, London Univ. Pp. 298. Baltimore: Williams & Wilkins. Price, \$5.00.

THIS short but comprehensive textbook of psychiatry comes to us from England. The psychoneuroses, epilepsy, mental disorders and mental defects are described in successive chapters. In addition, there are chapters on psychopathology, psychotherapy, and the legal aspects of psychiatry. The author, who appears to have a special interest in mental deficiency, expresses this orientation by espousing the idea that "germ corruption" or blastophoria, is a causative factor in psychiatric disorders. He makes much of terms such as "constitutional mental instability," "constitutional predisposition" (to mental disease), "poor mental stamina," etc. He warns against psychoanalysis, and dismisses Freud as one whose work, although having a revivifying effect, largely consisted in the bestowal of new names on old concepts. "Unfortunately," he adds, "Freud seems to have been obsessed by sex." There is a section on neuroses and psychoses in soldiers, which is also marred by the author's reactionary psychopathologic theories.

D. P.

THE MANAGEMENT OF NEUROSYPHILIS. By BERNHARD DATTNER, M.D., JUR.D., Associate Clinical Professor of Neurology, New York Univ. Medical College. With the collaboration of EVAN W. THOMAS, M.D., and GERTRUDE WEXLER, M.D. Foreword by JOSEPH EARLE MOORE, M.D. Pp. 398; 40 figs., charts, tables. New York: Grune & Stratton, 1944. Price, \$5.50.

In the first part, the Author discusses the techniques of withdrawing and examining spinal fluid and the interpretation and evaluation of changes occurring therein. He brings support to those who believe that spinal punctures can be safely done on the ambulatory patient. His experience has been that, providing the puncture is skilfully done with a narrow gauge needle (he prefers his double needle) and 10 cc. or less of fluid is removed, the patient has less chance of a headache if he remains active.

He emphasizes that changes in the spinal fluid are frequently found without clinical manifestations, and that there is no constant spinal fluid picture diagnostic of particular clinical entities. Dattner agrees with other workers on syphilis that the age of the infection and the influence of treatment are important factors in the prognostic interpretation of spinal fluids. He states that the finding of a negative spinal fluid in a case of at least 4 years' duration, and untreated for 6 months prior to the examination, is almost absolutely certain to remain negative.

In the second part the Author discusses all the methods of treating neurosyphilis. Some forms with meningeal involvement respond well to ordinary intensive chemotherapy. He favors fever therapy, preferably with malaria, followed by intensive chemotherapy for a short period for such cases that prove resistant to the above, and as first choice in the more serious types of cerebrospinal involvement. If the febrile response to malaria is good, he favors from 8 to 10 paroxysms, followed immediately by 10 daily injections of 0.06 gm. of mapharsen.

This book is interesting and easy to read. It reviews the subject in comprehensive manner and should be useful to anyone working in the field of neurosyphilis.

R. R.

THE ART OF ANÆSTHESIA. By PALUEL J. FLAGG, M.D., Visiting Anesthetist to Manhattan Eye and Ear Hosp.; Consulting Anesthetist to St. Vincent's Hosp., New York, N. Y.; Consulting Anesthetist to the Women's Hosp., Sea View Hosp., Jamaica Hosp., Mount Vernon Hosp., Flushing Hosp., Mary Immaculate Hosp., St. Mary's Hosp., Far Rockaway, N. Y.; Nassau Hosp., L. I.; Director of Pneumatology, World's Fair, New York City, and Chairman of Committee on Asphyxia of the American Medical Association. Seventh Ed. Pp. 519; 166 illus. Philadelphia, London, Montreal: J. B. Lippincott Company, 1944. Price, \$6.00.

THIS book is in no sense a comprehensive treatment of the subject. The Author's known preference for ethyl ether is evident throughout. Some of the major advances in anesthesia such as the technique of continuous spinal, the use of pentothal intravenously, and of cyclopropane by inhalation are dismissed as innovations or as being too recent for evaluation. While no one can deny the widespread usefulness of ether, unless it be clearly regarded as one individual's personal opinion, a text on anesthesia should be broader in scope, and more tolerant. Spinal anesthesia is a valuable adjunct to surgery and anesthesia, yet this commonly employed method is treated in 13 sketchy pages.

Despite the imbalance of the presentation, it is interesting to read of the Author's experience with ether. His approach to the signs of anesthesia is quite different from the standard, yet the careful student can learn much, for the topic is covered in detail. As a record of personal feelings, the volume can be recommended, but as a broad approach to the field of anesthesia, there are omissions which can be questioned.

R. D.

A TEXTBOOK OF HISTOLOGY. Arranged Upon an Embryological Basis. By J. LEWIS BREMER, M.D., Hersey Professor of Anatomy, Harvard Univ. Rewritten by HAROLD WEATHERFORD, Ph.D., Assistant Professor of Anatomy, Harvard Univ. Sixth Ed. of "Lewis and Stohr." Pp. 723; 598 illus. Philadelphia: Blakiston, 1944. Price, \$7.00.

THE material covered in this new edition embraces the whole meeting ground of Histology and Embryology. The traditional aspects of Histology have not been neglected but the ideas of previous authors are supplemented with a vast amount of information collected from the works of investigators of recent years. The classical point of view and modern ideas are brought successfully into harmony. Fundamental questions on Embryology are very clearly presented. Over 300 new carefully selected and very instructive figures have been added in this edition.

In every part and detail this is a modern textbook of Histology and may be recommended to medical students and to physicians as a good reference book for their bookshelf.

The authors, co-authors and the publishers have produced a book that will be very popular among students and teachers in Histology.

G. DE R.

PRINCIPLES AND PRACTICES OF INHALATIONAL THERAPY. By ALVAN L. BARACH, M.D., Associate Professor of Clinical Medicine, Columbia College of Physicians and Surgeons; Assistant Attending Physician, Presbyterian Hospital. Pp. 315; 59 figs. Philadelphia: J. B. Lippincott, 1944. Price, \$4.00.

THIS, the first volume of its kind in medical literature, is written by one who has pioneered in the field of inhalation therapy. The physiologic basis

for such treatment is thoroughly presented in chapters dealing with pneumonia, pulmonary edema, coronary artery disease, atelectasis, asthma and emphysema. The implications of anoxia are also stressed in a number of conditions with which physicians are less familiar, *e. g.*, blast injuries, caisson disease, aerial transportation, head injuries, fever therapy. Practical details are given in addition to the excellent theoretical discussions. The various methods of inhalation therapy are outlined. A chapter on respirators is useful. Positive pressure techniques, the use of nebulized solutions of various drugs and other recent advances in the treatment of respiratory disorders are all carefully presented.

The book should prove stimulating to the respiratory physiologist, internist, anesthetist and surgeon.

R. D.

UROLOGICAL SURGERY. By AUSTIN INGRAM DODSON, M.D., F.A.C.S., Professor of Urology, Medical College of Virginia; Urologist to the Hospital Division, Medical College of Virginia; Urologist to Crippled Children's Hospital, St. Elizabeth's Hospital, St. Luke's Hospital and McGuire Clinic. With contributions by 7 well-known authorities. Pp. 768; 576 illus. St. Louis: C. V. Mosby, 1944. Price, \$10.00.

SPECIAL emphasis on the surgical treatment of urologic conditions is made in this new book. The author states that his purpose is to present information on surgical problems arising in practice, as a surgical supplement to the many excellent books already written on the principles and practice of urology.

Anatomy of the genito-urinary tract, with special reference to surgical considerations, is presented. Throughout the text, preoperative and post-operative treatment, so essential to good results in urologic surgery, is emphasized. There are chapters on excretion urography and cystography, radiation therapy, acid-base balance, fluid administration, blood transfusion, anesthesia, and endocrinology. Each of these chapters is written by an author who is a specialist in the respective field. Surgical problems are discussed in anatomic sequence, beginning with the kidney and followed by adrenal, ureter, bladder, urethra, perineum, penis, scrotum and testicle. Diseases of the adult male and female, as well as diseases in children are presented.

Illustrations are good. Those showing the technic of certain operative procedures are particularly well presented. Each chapter is followed by a bibliography. References are made to the most recent literature.

This book should be of particular value to urologists, and general surgeons; it should also be an excellent reference book for medical students and general practitioners.

L. LaT.

THE ART AND SCIENCE OF NUTRITION. A Textbook on the Theory and Application of Nutrition. By ESTELLE H. HAWLEY, Ph.D., and GRACE CARDEN, B.S., The Univ. of Rochester, School of Medicine and Dentistry, Strong Memorial and Rochester Municipal Hospitals, Rochester, N. Y. Second Ed. Pp. 668; 139 illus. (11 colored); 138 figs.; 68 tables. St. Louis: C. V. Mosby, 1944. Price, \$3.75.

As the title suggests, this book deals not only with the basic principles of nutrition, but also goes into great detail to demonstrate how best to apply the principles to everyday living and to the special needs of diet therapy.

It is focussed especially on teaching of dietetics in schools of nursing, but it would be a most useful reference book for the practitioner of medicine as well. One section of the book is devoted to food requirements under special conditions, such as pregnancy and its complications, lactation, the feeding of infants and young children, diet in relation to the teeth, and the food requirements of old age. Diet therapy is treated at length. A practical laboratory course of 20 lessons on the choice, preparation, and serving of foods is included. Illustrations are numerous and excellent.

E. W.

FERTILITY IN MEN. By ROBERT SHERMAN HOTCHKISS, B.S., M.D., LT. COMM. (M.C.), U.S.N.R. (on active service), Assistant Professor of Urology, New York Univ. Medical College; Instructor in Surgery (Urology), Cornell Medical College; Assistant Visiting Attending Physician, Department of Urology, Bellevue Hospital; Assistant Visiting Attending Physician in Surgery (Urology), New York Hospital; Chief of Urological Clinic, New York Univ. Medical College Clinic. Foreword by NICHOLSON J. EASTMAN, M.D. Pp. 216; 95 illus. Philadelphia: J. B. Lippincott, 1944. Companion book to "Fertility in Women." Price, in slip case, \$8.00.

THE book presents a clinical study of the causes, diagnosis, and treatment of impaired fertility in the male. It is issued as a companion volume to "Fertility in Women," by S. L. Siegler.

Until recent years the blame for sterility in marriage was almost always placed on the wife. However, during the past 2 decades accumulative information would indicate that many cases of sterility in a family group are due to diseases in the male. The discovery that sterility in the male was widespread opened a new field of study and treatment in urology. This volume presents such information on the problems associated with male sterility in a concise, well-organized manner.

With special reference to fertility, anatomy, physiology, and pathology of the male genital organs are discussed. Much new information on the metabolism of spermatozoa and the chemical composition of semen is presented. Practical methods of increasing fertility in the male are recorded. The techniques and laboratory studies of spermatozoa and semen are given in detail. No other reference book need be consulted in order to carry out such methods satisfactorily. There are several case histories illustrating various types of sterility and emphasizing not only the anatomic-pathologic entities, but also the psychic aspects of cases besides. Medical and surgical methods of treatment of the various entities are discussed in detail. Excellent illustrations appear and each chapter is followed by a liberal bibliography.

Future therapy in diseases causing sterility depends on advances in glandular physiology, enzymic chemistry, nutrition, and cytology. Advances in the laboratory must be applied to treatment of the patients. Sterile patients, successfully treated, are most grateful.

L. La T.

THE ROMANCE OF MEDICINE. The Story of the Evolution of Medicine From Occult Practices and Primitive Times. By BENJAMIN LEE GORDON, M.D., Member, Am. Assn. of the Hist. of Med.; Attending Ophthalmologist to the Shore Memorial Hospital, Somers Point, N. J., and to Atlantic County Hospital for Tuberculosis, Northfield, N. J. Authorized Medical Examiner for Civil Aeronautics Administration, Dept. of Commerce, Washington, D. C. Formerly Associate Ophthalmic Surgeon of St. Agnes Hospital of Philadelphia. Pp. 624; 147 illus. Philadelphia: F. A. Davis, 1944. Price, \$5.00.

THOUGH this entertaining volume touches throughout on medical matters from the historical point of view, it is in no sense a history of medicine, whether biographic, topic, or chronologic—nor is it intended to be so. Starting with primitive man's concepts of life and disease, the author aims to trace the evolution of these concepts into the corresponding ideas of today. This plan leads to 26 chapters on such subjects as Fecundation and Gestation, Galenic Physiology, The Vital Principle, Demonology, Astrology, The Evil Eye, Spiritual Healers, Scapegoats, Mystic Medicine, "Signatures," Primitive Healing Measures, Ancient Ethics, Ideas of After Life. One might infer from such a list that superstitions would fill most of the book. Not only is this the case, but in telling about them the author is at his best; the change to a brief consideration of modern practices usually being more of a jump than a gradual progress.

One adds regretfully that illustrations are mostly on hackneyed subjects and are poor specimens, also that there is but little use of original sources; and one who is annoyed by poor spelling will be frequently annoyed. (The Reviewer found 18 such errors in less than an hour's reading.) Nevertheless, the book contains much interesting information about primitive and ancient customs related to medicine, and should afford pleasant and instructive reading to those curious about such matters.

E. K.

FERTILITY IN WOMEN. By SAMUEL L. SIEGLER, M.D., F.A.C.S., Attending Obstetrician and Gynecologist, Brooklyn Women's Hospital; Attending Gynecologist, Unity Hospital; Assistant Obstetrician and Gynecologist, Greenpoint Hospital; Attending Sterility Clinic, Greenpoint Hospital; Consultant in Gynecology, Rockaway Beach Hospital; Diplomate, Am. Board of Obstetrics and Gynecology; Fellow, New York Academy of Medicine; Member, Soc. for the Study of Internal Secretions. Foreword by ROBERT LATOU DICKINSON, M.D. Pp. 450; 194 illus. Philadelphia: J. B. Lippincott, 1944. Companion book to "Fertility in Men." Price, in slip case, \$8.00.

THIS treatise on the causes, diagnosis, and treatment of impaired fertility in the female is a companion volume to "Fertility in Men," by R. S. Hotchkiss, M.D. A consideration of the problems associated with both male and female aspects of sterility, the author's so-called "bilateral approach" is stressed throughout the book.

Knowledge of the factors responsible for both male and female fertility has advanced considerably in the past 2 or 3 decades. Studies in the biology, chemistry, physiology, and psychiatry of human reproduction and sex adjustments have aided greatly in furthering this knowledge. Methods of evaluating fertility in the laboratory, as well as special points in history taking and physical examination are presented. This information would enable one to make a true evaluation of the case at hand.

There are chapters on the physiology of the female sex cycle, cervical and vaginal secretions and their relation to spermatozoa, and tubal factors in sterility. Endocrine disorders in which sterility occurs are thoroughly discussed. The present methods of medical and surgical treatment of such conditions as are amenable to therapy are discussed.

The purpose of the book is to present a description of the anatomic and physiologic factors in sterility encountered in medical practice. It covers the subject of the females' part in sterility completely, and along with its companion volume, "Fertility in Men," makes an important contribution to recorded knowledge on this subject.

L. LaT.

THE MEDICAL CLINICS OF NORTH AMERICA, March, 1944. Symposium on Chronic Diseases. Pp. 516. Philadelphia and London: W. B. Saunders. Price, \$16.00, year.

THE contributors to this volume show a practical, lucid, and up-to-date approach to the subjects chosen, place much emphasis on treatment, and have succeeded to an unusual degree in combining the newer therapeutics with such older methods of treatment as have stood the test of time.

The introduction by R. L. Cecil makes clear the prevalence of chronic disease in the younger age groups. Far from finding chronicity synonymous with old age, we discover in the New York City studies that nearly half the chronically ill patients were under 40 years of age, about a third being children under 16.

Discussions on present-day treatment of *syphilis* and of *gonorrhea* occupy the first and the last places in this volume. Experience now accumulated with short-term arsenotherapy is reviewed. A rational treatment for gonor-

rhea, combining the use of sulfonamides with older forms of treatment, is outlined. In both of these discussions one catches a hint of the temporary, and the impression that penicillin, when generally available, may be the answer to the search for a quick treatment for early syphilis and for gonorrhea.

Chronic arthritis is the most prevalent of all chronic ailments. For *rheumatoid arthritis*, various forms of therapy are evaluated, and especially the results to date of therapy with vitamin D and with gold. The dangers of toxic manifestations are outlined.

Accepted methods for treating chronic diseases of nose, throat and ear are presented. A few well-chosen case reports serve to illustrate pitfalls in the diagnosis and treatment of diseases of the larynx and trachea. Treatment for the refractive case of *bronchial asthma* is detailed, including methods of inducing cumulative relaxation of the bronchial musculature by repeated use of aminophyllin intravenously or by rectum.

An especially helpful paper dealing with the chronic anemias points out the fallacy of attempts at treatment without proper diagnosis, and gives in outline form the studies required for adequate diagnosis, and the classification of the anemias based on etiology and morphology. A brief paper on *renal insufficiency* usefully directs attention to reversible causes and the importance of search for such causes in all cases not definitely assignable to the irreversible group.

The medical management of *peptic ulcer* is discussed on the basis of a large clinical experience. Simplification of treatment to the point where the average patient relies primarily on food and mode of life, and little or not at all on medication, will be found a boon to patient and physician alike. *Functional disturbances of the alimentary tract* are reviewed. There are helpful discussions on the management of *heart disease*; the management of *diseases of the nervous system*, and *chronic endocrine disorders*, including a special paper on the difficult problem of exophthalmos in Graves' disease.

Not the least useful feature of the whole collection of papers is the carefully selected list of references attached to each. The physician will find this volume a convenient and reliable guide and will welcome the wealth of practical suggestions for the handling of some of man's most difficult ailments.

J. M.

INTRAVENOUS ANESTHESIA. By R. CHARLES ADAMS, M.D., C.M., M.S. (ANES.), Associate in Section on Anesthesiology, Mayo Clinic; Instructor in Anesthesiology, Graduate School University of Minnesota, Rochester, Minn. Foreword by Dr. JOHN S. LUNDY. Pp. 663; 34 tables; 75 figs. New York, London: Paul B. Hoeber, 1944. Price, \$12.00.

This book gathers under one cover a good bit of interesting and useful information about the intravenous administration of various narcotics. Ether, paraldehyde, alcohol, and magnesium sulfate, have all been used in the past and occasional clinical articles are appearing now suggesting their value in various conditions. It is helpful to have detailed reference to the earlier development and present status of these agents. Incidentally, one would expect more data on the intravenous use of morphine.

The book represents an unusual attempt to review apparently every article ever written on the subject. In an introductory chapter on derivatives of barbituric acid, for example, 498 references are listed! In a chapter on Pernoston, a drug rarely used today, 303 articles are given. The intravenous anesthetic most commonly used in this country is pentothal sodium, and this agent is not considered until page 451. Whether the importance of the field justifies so inclusive a coverage remains for the individual leader to determine. It is perhaps doubtful as to whether 662 pages are necessary to adequately review the topic. In the preface the Author points out his awareness of the detailed nature of the presentation so that the Reviewer's criticisms are perhaps unjust.

R. D.

THE YOUNGEST OF THE FAMILY. HIS CARE AND TRAINING. A Manual for the Inexperienced Mother. By JOSEPH GARLAND, M.D., Physician to Children's Med. Dept., Massachusetts General Hospital; Consulting Pediatrician, Massachusetts Eye and Ear Infirmary; Instructor in Pediatrics, Harvard Medical School. Revised Ed. Pp. 182. Cambridge, Mass.: Harvard Univ. Press, 1943. Price, \$2.00.

DR. GARLAND is practical, conservative, learned and witty; and his "baby-raising" book is a polished expression of current pediatric thought. Advice on the many maneuvers of baby care is given in literary rather than cookbook style, which no doubt will confuse some readers and please others. The major defect in the presentation is the absence of a section on the preparation of milk mixtures and the sterilization of feeding equipment. Emphasis has been directed toward building up an understanding of the phenomena of infant and pre-school child behavior. This is, of course, of paramount importance, and the book may be recommended with assurance to intelligent parents who are desirous of that type of guidance. I. W.

THE PATHOGENESIS OF TUBERCULOSIS. By ARNOLD R. RICH, M.D., Associate Professor of Pathology, The Johns Hopkins University School of Medicine, Baltimore, Md. Pp. 1008; 89 figs.; 4 charts; 20 tables. Springfield, Ill.: Charles C Thomas, 1944. Price, \$10.50.

RESEARCH in tuberculosis has progressively built up a tremendous literature over many years. Many of the older concepts have been amended or supplanted. Others, on which the evidence is still incomplete, or worse, contradictory, are in a state of flux. Because of his special interest in tuberculosis and his fine anatomic background, the author is admirably suited to attack this problem. He has produced a most valuable survey of the field with critical reevaluation of many long accepted fundamental concepts.

The book begins with a discussion of the tubercle bacillus, its mode of action, as a whole and as isolated chemical fractions. Next, a large section is given over to the immunologic aspects of the disease, native and acquired resistance and hypersensitivity. Following this, in a discussion of the factors responsible for the tuberculous lesion, he gives a good account of the general pathologic anatomy and later, in a separate chapter, considers the special pathologic anatomy of certain organs (lung and meninges). As the emphasis is placed on pathogenesis no extensive anatomic descriptions are attempted.

The text reads easily despite profuse documentation. Throughout is evident the special care taken to provide references. The extensive bibliography (1417 references) should prove most valuable to those with special interest in any of the various controversial problems. The sections on resistance and hypersensitivity are recommended to students, teachers, and practitioners, as they help to clarify this complex subject. Especially convenient are the short summaries at the end of each section.

The book's most important contribution is that it provides the urgently needed correlation between the massive animal experimental researches and the disease as it occurs in man. W. S.

HYPERTENSION AND HYPERTENSIVE DISEASE. By WILLIAM GOLDRING, M.D., Associate Professor of Medicine, New York Univ. College of Medicine; and HERBERT CHASIS, M.D., Assistant Professor of Medicine, New York Univ. College of Medicine. Pp. 253; 53 figs.; 27 tables. New York: The Commonwealth Fund, 1944. Price, \$3.50.

For those interested in keeping abreast of current thought regarding the nature of hypertension, this book will prove well worth reading. The authors review the pioneer clinical work in the study of differential aspects of renal physiology which they, in association with Dr. Homer W. Smith, have performed. Further, they present their present concept of hypertensive disease and its various ramifications.

The book is divided into short, readable chapters. Illustrations and references are well chosen. Investigative techniques are described in sufficient detail to guide those who may wish to employ the elaborate, but ingenious procedures which these workers have developed. The authors conclude that no treatment yet devised is of avail in altering the slow but certain course of hypertensive disease.

W. J.

SYSTEMATIC INORGANIC CHEMISTRY—THE FIFTH AND SIXTH GROUP NON-METALLIC ELEMENTS. By DON M. YOST, Professor of Inorganic Chemistry, and HORACE RUSSELL, JR., Instructor in Chemistry, California Institute of Technology. Pp. 423; 78 figs.; 109 tables. New York: Prentice-Hall, 1944. Price, \$4.60.

In this book the authors have selected a list of topics devoted to the fifth and sixth group non-metallic elements of the periodic system and "include in the discussion of each enough of the old and the new chemistry to bring out the most important features of the substances." In many cases the original literature references are included in the statements throughout the text. These guide the student seeking a detailed discussion of the point in question.

The methods of preparation and purification of the various substances are given. Both physical and chemical properties are included. Figures and tables, giving other pertinent data, are numerous.

In addition, the authors emphasize "the research point of view" by suggesting "many problems worthy of the serious attention of research workers."

The scope of the book as given by chapter headings follows: 1. Nitrogen and Its Oxides and Sulfides. 2. Nitrogen Oxyhalides and Oxyacids; Fixation of Nitrogen. 3. Hydroxylamine, Amine Sulfonites, Phosphorus Chloronitrides, Hydrazine, and Hydrazoic Acid. 4. Ammonia and Liquid Ammonia Solutions. 5. Phosphorus, Its Oxides and Sulfides. 6. Oxyacids of Phosphorus. 7. Phosphorus Halides and Oxyhalides; Phosphine. 8. Oxygen, Sulfur, Selenium, Tellurium, and Their Compounds With Hydrogen. 9. Halides and Oxyhalides of Sulfur, Selenium, and Tellurium. 10. Oxides and Oxyacids of Sulfur, Selenium, and Tellurium. 11. Hydrogen Peroxides, Persulfides, and Peroxyacids; Metallic Peroxides and Superoxides; Polythionic Acids.

In the Appendices are listed a bibliography of reference books, general physical constants, and the periodic system of elements.

The volume is well printed and easy to read. It contains complete subject and name indices. For a study of the specialized field of inorganic chemistry (fifth and sixth group non-metals) this book will serve as an excellent textbook or reference text.

C. D.

REBEL WITHOUT A CAUSE. The Hypnoanalysis of a Criminal Psychopath. By ROBERT M. LINDNER, PH.D., U. S. Public Health Service (R) Psychologist, U. S. Penitentiary, Lewisburg, Pa.; Lecturer in Criminology, Bucknell Univ. Introduction by SHELDON GLUECK, LL.B., PH.D., Professor of Criminal Law and Criminology, Law School, Harvard Univ., and ELEANOR T. GLUECK, Ed.D., Research Criminologist, Law School, Harvard Univ. Pp. 295. New York: Grune & Stratton, 1944. Price, \$4.00.

By combining the methods of psychoanalysis and hypnotism, this psychologist has evolved an original plan for the study of psychopathy as encountered in psychiatry and criminology. The method is termed hypnoanalysis, and is defined as "a radically abbreviated method for the investigation of the personality and the treatment of psychogenic disorders and aberrations of behavior." In speaking of the method, the writers of the Introduction state that they do not "know whether . . . it will go beyond diagnostic dissection to permanent reconstruction of the personality."

The subject studied was in good health, except that following an attack of measles in infancy, he was left with what one specialist termed *nystagmus*

amblyopia, and another, *congenital defective retinae*. Disclosure of the lad's psychopathic personality came through the commission of numerous delinquencies and one stabbing affair. After taking a formal case history, the hypnotized subject's revelations were recorded during 46 sittings of 1 hour each. For the ready attainment of the trance state it is said a week may be required, but that, later, the state should be attained almost at once. After the induction of complete amnesia, all resistance is overcome and disclosure flows smoothly as various components of the psychoanalytic technique are applied.

Somewhat apologetically, the writer explains that while only 1 case is here hypnoanalyzed, he has had 5 others which likewise "demonstrated . . . at least at the time of this writing of the benefits of treatment." In helping to solve the perplexing problem of the psychopathic personality, a courageous effort has been made through an original plan of analysis and reconstruction. A bibliography and index are included. N. Y.

ARTIFICIAL PNEUMOTHORAX IN PULMONARY TUBERCULOSIS. By T. N. RAFFERTY, M.D., formerly Resident Physician, William H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Mich. Introduction by HENRY STUART WILLIS, M.A., M.D. Pp. 192; 26 figs.; 14 tables. New York: Grune & Stratton, 1944. Price, \$4.00.

THE title of this book, not indicating the true scope of the work, is apt to deflect from its usefulness. Although primarily a discussion of artificial pneumothorax, it covers the whole subject of collapse therapy in tuberculosis. By discussing the pros and cons of the various types of collapse therapy, an overall picture of the treatment and prognosis of the disease is presented. This is valuable both to the specialist and to the internist or family physician who directs the care of the patient. The latter, unfortunately, is apt to have too optimistic a point of view as to the prognosis. This book will once more acquaint him with the true dangers of the disease and the need for careful supervision of all cases.

The chapters on the importance of bronchoscopic examination and closed intrapleural pneumolysis are particularly good. These procedures are not in general use and too often are neglected because of the technical skill required. The section on the management of pneumothorax is full and complete and yet not too technical to be tiring. In fact, the entire book is well written and the subject matter pleasantly presented. D. P.

QUICK REFERENCE BOOK OF MEDICINE AND SURGERY. A Clinical, Diagnostic, and Therapeutic Digest of General Medicine, Surgery, and the Specialties. By GEORGE E. REHBERGER, A.B., M.D. Twelfth Ed. Pp. 1460. Philadelphia, London, Montreal, J. B. Lippincott, 1944. Price, \$15.00.

THE fact that this book has reached its 12th edition in 24 years is good evidence of its continued popularity. Perhaps this is in measure to be explained by the relatively large amount of space devoted to methods of therapy. As regards the other aspects of medicine, surgery, and obstetrics the discussions are of necessity very sketchy. A physician with even a very modest library should have little need for books of this kind. H. S.

THE ANALYSIS AND INTERPRETATION OF SYMPTOMS. Edited by CYRIL M. MACBRYDE, M.D., and ten contributors. Reprinted from *Clinics*, Vol. 11, No. 6, 1944. Pp. 301; numerous figs., tables and plates. Philadelphia: J. B. Lippincott, 1944. Price, \$4.00.

THIS is an excellent book. Its excellence consists in its practical approach to clinical problems and the thoroughness with which each subject is presented. As MacBryde says in his introduction, a patient does not present

himself with a diagnosis but with a symptom. The ordinary textbook, however, classifies data according to diagnoses and not under symptom headings. Some older textbooks, like those of Butler and of French, adopted the latter system and were highly popular. This one should be more so because it does more than list the causes of nervousness, fatigue, headache, fever, cough, abdominal pain, etc.; it explains the mechanism involved, and in most instances this is done by one who has made significant contributions in the field that he presents. Many other symptoms and physical phenomena such as nausea, diarrhea, anemia, weight loss and lymphadenopathy, might well be the subjects for a subsequent presentation. Such books will appeal to medical students especially, but will also be welcomed by the practicing physician. Within themselves they are stimulating and they will lead to further intelligent perusal of the fundamental literature. T. M.

NEW BOOKS

Neurology of the Eye, Ear, Nose, and Throat. By E. A. SPIEGEL, M.D., Professor of Experimental and Applied Neurology and Head of Dept. of Experimental Neurology, Temple Univ. School of Med., and I. SOMMER, M.D., Lecturer in Ophthalmology, Long Island Coll. of Med.; Consultant Ophthalmologist and Otolaryngologist, Chicago Eye and Ear Hosp. Pp. 690; 118 figs. New York: Grune & Stratton, 1944. Price, \$7.50.

Gynecological and Obstetrical Urology. By HOUSTON S. EVERETT, A.B., A.M., M.D., Associate Professor of Gynecology, the Johns Hopkins Univ., and Associate in Gynecology, The Univ. of Maryland; Assistant Visiting Gynecologist and Gynecologist in charge of the Cystoscopic Clinic, the Johns Hopkins Hosp.; Visiting Gynecologist, the Church Home and Hosp., the Hosp. for the Women of Maryland, and the Union Memorial Hosp. Pp. 517; 220 figs. Baltimore: Williams & Wilkins, 1944. Price, \$6.00.

All About Feeding Children. By MILTON J. E. SENN, M.D., Associate Attending Pediatrician, New York Hosp., Associate Professor of Pediatrics in Psychiatry, Cornell Univ. Med. Coll., and PHYLLIS KRAFFT NEWILL. Pp. 269. New York: Doubleday, Doran & Co., 1944. Price, \$2.50.

Taber's Dictionary of Gynecology and Obstetrics. By CLARENCE WILBUR TABER, Medical Editor and Author of Taber's Cyclopedic Medical Dictionary, Taber's Condensed Medical Dictionary, and Dictionary of Food and Nutrition, etc. With the Collaboration of MARIO A. CASTALLO, M.D., F.A.C.S., Assistant Professor of Obstetrics, Jefferson Med. Coll.; Gynecologist to St. Mary's and St. Agnes' Hosp.; Obstetrician to St. Mary's Hosp.; Diplomate, American Board of Obstetrics and Gynecology, etc., etc. Pp. 706; numerous illus. Philadelphia: F. A. Davis, 1944. Price, \$3.50.

Proteins and Amino Acids. Physiology, Pathology, Therapeutics. By The Scientific Staff of the Arlington Chemical Company. Pp. 189. New York: Arlington Chemical Co., 1944.

Virus Diseases in Man, Animal and Plant. By GUSTAV SEIFFERT. A Survey and Reports Covering the Major Research Work Done During the Last Decade. Pp. 332. New York: Philosophical Library, 1944. Price, \$5.00.

The British Encyclopædia of Medical Practice Including Medicine, Surgery, Obstetrics, Gynecology and Other Special Subjects. Cumulative Supplement, 1944. Under the General Editorship of SIR HUMPHREY ROLLESTON, Bt., G.C.V.O., K.C.B., M.D., D.Sc., F.R.C.S., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge; Sometime President of The Royal Coll. of Physicians of London. Pp. 306. London: Butterworth & Co., 1944.

The British Encyclopædia of Medical Practice Including Medicine, Surgery, Obstetrics, Gynæcology and Other Special Subjects. Medical Progress, 1944. Under the General Editorship of SIR HUMPHREY ROLLESTON, Bt., G.C.V.O., K.C.B., M.D., D.Sc., F.R.C.S., D.C.L., LL.D., Emeritus Regius Professor of Physies, Cambridge; Sometime President of The Royal Coll. of Physieians of London. Pp. 537. London: Butterworth & Co., 1944.

NEW EDITIONS

Physiology in Health and Disease. By CARL J. WIGGERS, M.D., D.Sc., F.A.-C.P., Professor of Physiology and Director of Physiology Dept. in the School of Med. of Western Reserve Univ., Cleveland, Ohio. Fourth Ed. Pp. 1174; 274 figs. Philadelphia: Lea & Febiger, 1944. Price, \$10.00.

A Method of Anatomy. Descriptive and Deductive. By J. C. BOILEAU GRANT, M.C., M.B., CH.B., F.R.C.S. (EDIN.), Professor of Anatomy in the Univ. of Toronto. Third Ed. Pp. 822; 729 figs. Baltimore: Williams & Wilkins, 1944. Price, \$6.00.

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